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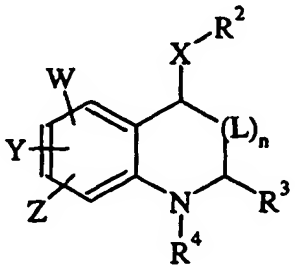
(54) Title: TETRAHYDROQUINOLINE DERIVATIVES AS STAT6-MODULATORS, PREPARATION AND USE THEREOF



(I)

(57) Abstract: Compounds of formula (I) are modulators of STAT6 signal pathway activity, and can be used in the treatment of atopic dermatitis, urticaria, allergic asthma, allergic rhinitis, a food allergy, allergic conjunctivitis, hayfever, bullous pemphigoid, industrial sensitization, chronic rejection of transplants or COPD.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TETRAHYDROQUINOLINE DERIVATIVES AS STAT6-MODULATORS, PREPARATION AND USE THEREOF

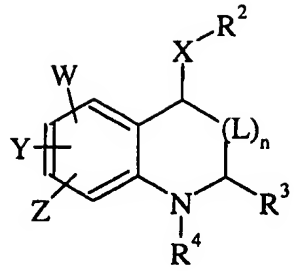
The present invention relates to tetrahydroquinoline derivatives which are modulators of the Signal Transducer and Activator of Transcription 6 (STAT6) pathway, to processes for their preparation, to pharmaceutical compositions comprising them and to methods of using them (for example for the treatment of STAT6-mediated diseases).

STATs are proteins involved in signal transduction from cytokine and growth factor receptors. STAT6 binds to specific phosphotyrosine motifs on an activated IL-4/IL-13 receptor α-chain. Once bound, the protein is phosphorylated by JAK kinases and then STAT6 forms a homodimer that translocates into the nucleus and stimulates gene transcription. Gene knockout studies in mice have shown that STAT6 is required for IL-4/IL-13 responses that have pathological consequences in allergic disease, namely IgE production and differentiation of T helper cells to the Th2 phenotype. (Linehan LA. Warren WD. Thompson PA. Grusby MJ. Berton MT. STAT6 is required for IL-4-induced germline Ig gene transcription and switch recombination. *Journal of Immunology. 161(1):302-10, 1998*; Kaplan MH. Schindler U. Smiley ST. Grusby MJ. Stat6 is required for mediating responses to IL-4 and for development of Th2 cells. *Immunity. 4(3):313-9, 1996*; Malabarba MG. Rui H. Deutsch HH. Chung J. Kalthoff FS. Farrar WL. Kirken RA. Interleukin-13 is a potent activator of JAK3 and STAT6 in cells expressing interleukin-2 receptor-gamma and interleukin-4 receptor-alpha. *Biochemical Journal. 319 (Pt 3):865-72, 1996.*)

Interference with STAT6 activation would be expected to reduce the production of proinflamatory cytokines like IL-4 and IL-5. A compound antagonizing STAT6 would, therefore, be expected to have utility in treating disease states such as asthma, dermatitis (allergic and atopic), urticaria, rhinitis and/or COPD.

1,2,3,4-Tetrahydroquinolines are disclosed in WO 00/17165 and WO 00/17166.

The present invention provides a compound of formula (I):



(I)

wherein:

L is CH_2, O or S;

n is 0 or 1;

W, Y and Z are, independently hydrogen, cyano, nitro, halogen, N_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONR^5R^6$, COR^{10}, SO_2R^{12}, methylenedioxy, $NHCOR^{11}$ or heterocyclyl;

R^2 is aryl or heteroaryl optionally substituted by cyano, nitro, halogen, N_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONR^{13}R^{14}$, COR^{15}, SO_2R^{16}, methylenedioxy, $NHCOR^{17}$ or heterocyclyl;

R^3 is C_{1-4} alkyl or C_{1-4} haloalkyl;

R^4 is $CO(C_{1-4}$ alkyl) or $CO(C_{1-4}$ haloalkyl);

X is O, S, SO, SO_2, CR^7R^8 or NR^9;

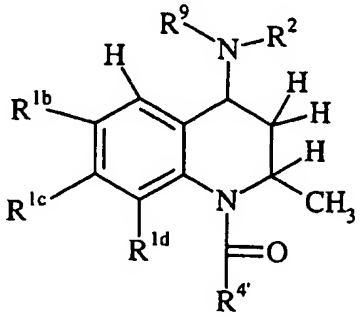
R^5, R^6, R^7, R^8, R^{13} and R^{14} are, independently, hydrogen or C_{1-6} alkyl;

R^9 is hydrogen, C_{1-6} alkyl or $CO(C_{1-4}$ alkyl);

R^{10}, R^{11}, R^{12}, R^{15}, R^{16} and R^{17} are, independently, C_{1-6} alkyl or phenyl;

or a pharmaceutically acceptable salt thereof; or a solvate thereof;

provided that the compound of formula (I) is not a compound of formula (Iz):



(Iz)

wherein

R^{1b}	R^{1d}	R^{1c}	$R^{4'}$	R^2	R^9
H	H	H	n-butyl	C_6H_5	H
H	H	H	n-propyl	C_6H_5	$COCH_3$
H	H	H	n-propyl	C_6H_5	H
H	H	H	Ethyl	C_6H_5	H
Br	H	H	Methyl	C_6H_5	$COCH_3$
Methyl	H	H	Methyl	4-CH_3-C_6H_4	H
Methyl	Methyl	H	Methyl	2,4-$(CH_3)_2$-C_6H_3	H
H	H	H	Methyl	C_6H_5	H
NO_2	H	H	Methyl	4-NO_2-C_6H_4	$COCH_3$
NO_2	H	H	Methyl	C_6H_5	$COCH_3$
Cl	H	H	Methyl	C_6H_5	$COCH_3$
H	H	H	Methyl	C_6H_5	$COCH_3$
H	H	H	Methyl	2,4-Br_2-C_6H_3	$COCH_3$

in free base or unsolvated form.

Alkyl groups are straight or branched chain and are, for example, methyl, ethyl, n-propyl, iso-propyl or n-butyl. Alkoxy is, for example, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy or tert-butoxy.

Cycloalkyl is, for example, cyclopropyl, cyclopentyl or cyclohexyl.

Halogen includes chlorine, fluorine and bromine.

Haloalkyl groups peferably comprise fluorine, chlorine or bromine atoms, and haloalkyl is, for example, CF_3, while haloalkoxy is, for example, OCF_3.

Aryl is, for example, phenyl or naphthyl.

Heteroaryl is, for example, an aromatic monocyclic 5- or 6-membered ring comprising one, two or three heteroatoms selected from the group comprising nitrogen, oxygen and sulphur. Heteroaryl is, for example, pyridine, pyridazine, pyrimidine, pyrazine, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, furan, thiophene, oxazole, isoxazole, thiazole or isothiazole.

Heterocyclyl is a 5- or 6-membered ring comprising one or two nitrogen atoms and, optionally, one oxygen or sulphur atom. Heterocyclyl is, for example, morpholinyl,

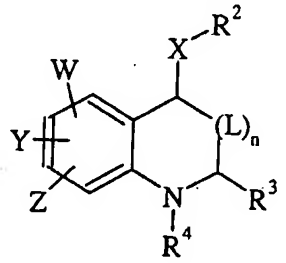
piperidinyl or pyrrolidinyl. Heterocyclyl may also be thiomorpholinyl. Heterocyclyl is optionally substituted by C_{1-4} alkyl.

Salts of the compounds of formula (I) are preferably pharmaceutically acceptable salts. Pharmaceutically acceptable salts of compounds of the present invention are, for example, acid addition salts (such as hydrochloride, hydrobromide or acetate salts).

Solvates of the compounds or salts of the present invention are conveniently hydrates, such as monohydrates or dihydrates.

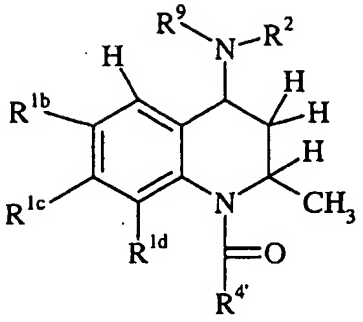
Compounds of the present invention include all stereoisomers and mixtures thereof in all proportions.

In one particular aspect the present invention provides a compound of formula (I):



(I)

wherein: L is CH_2, O or S; n is 0 or 1; W, Y and Z are, independently hydrogen, cyano, nitro, halogen, N_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONR^5R^6$, COR^{10}, SO_2R^{12}, methylenedioxy, $NHCOR^{11}$ or heterocyclyl; R^2 is aryl or heteroaryl optionally substituted by cyano, nitro, halogen, N_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONR^{13}R^{14}$, COR^{15}, SO_2R^{16}, methylenedioxy, $NHCOR^{17}$ or heterocyclyl; R^3 is C_{1-4} alkyl or C_{1-4} haloalkyl; R^4 is $CO(C_{1-4}$ alkyl) or $CO(C_{1-4}$ haloalkyl); X is O, S, SO, SO_2, CR^7R^8 or NR^9; R^5, R^6, R^7, R^8, R^{13} and R^{14} are, independently, hydrogen or C_{1-6} alkyl; R^9 is hydrogen, C_{1-6} alkyl or $CO(C_{1-4}$ alkyl); R^{10}, R^{11}, R^{12}, R^{15}, R^{16} and R^{17} are, independently, C_{1-6} alkyl or phenyl; or a pharmaceutically acceptable salt thereof; or a solvate thereof; provided that the compound of formula (I) is not a compound of formula (Iz):



(Iz)

wherein

R^{1b}	R^{1d}	R^{1c}	$R^{4'}$	R^2	R^9
H	H	H	n-butyl	C_6H_5	H
H	H	H	n-propyl	C_6H_5	$COCH_3$
H	H	H	n-propyl	C_6H_5	H
H	H	H	Ethyl	C_6H_5	H
Br	H	H	Methyl	C_6H_5	$COCH_3$
Methyl	H	H	Methyl	4-CH_3-C_6H_4	H
Methyl	Methyl	H	Methyl	2,4-$(CH_3)_2$-C_6H_3	H
H	H	H	Methyl	C_6H_5	H
NO_2	H	H	Methyl	4-NO_2-C_6H_4	$COCH_3$
NO_2	H	H	Methyl	C_6H_5	$COCH_3$
Cl	H	H	Methyl	C_6H_5	$COCH_3$
H	H	H	Methyl	C_6H_5	$COCH_3$
H	H	H	Methyl	2,4-Br_2-C_6H_3	$COCH_3$
H	H	Methyl	Methyl	4-C_2H_5-C_6H_4	H
H	H	H	Methyl	C_6H_5	CO-n-propyl
H	H	H	Methyl	C_6H_5	CO-t-butyl
H	H	H	CH_3CH-CH_3	C_6H_5	H
H	H	H	CF_3	C_6H_5	$COCF_3$
H	H	H	Ethyl	C_6H_5	$COCH_3$
H	H	H	iso-Pr	C_6H_5	$COCH_3$
H	H	H	iso-Pr	C_6H_5	H
H	H	H	Methyl	C_6H_5	CO-n-butyl

H	H	H	Methyl	C_6H_5	CO-ethyl
H	H	H	n-butyl	C_6H_5	$COCH_3$
H	H	H	Methyl	C_6H_5	CO-i-propyl
H	H	H	Ethyl	C_6H_5	CO-ethyl
H	H	H	CH_3CH_2	C_6H_5	H

in free base or unsolvated form.

In another aspect of the invention W and Y are both hydrogen. In yet another aspect W, Y and Z are, independently, for example, hydrogen, chloro, cyano, $CO_2(C_{1-4}$ alkyl) (such as CO_2Me or CO_2Et) or C_{1-4} alkoxy (such as methoxy).

In a further aspect R^2 is, for example, optionally substituted phenyl, such as phenyl optionally substituted by chloro, cyano, $CO_2(C_{1-4}$ alkyl) (such as CO_2Me or CO_2Et) or C_{1-4} alkoxy (such as methoxy).

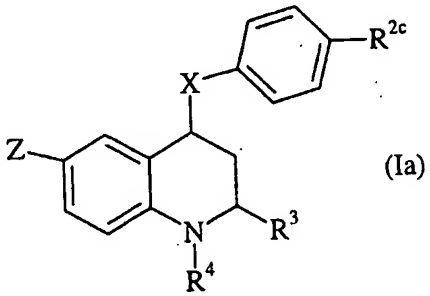
The variable R^3 is, for example methyl or ethyl; but is preferably methyl.

The variable R^4 is, for example, acetyl.

The variable X is, for example, NR^9, wherein R^9 is hydrogen or COMe.

It is preferred that L is CH_2 and that n is 1.

In a still further aspect the present invention provides a compound of formula (Ia):



(Ia)

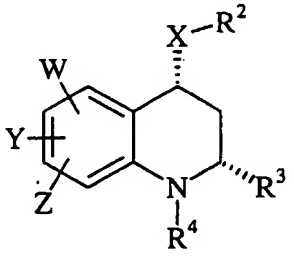
wherein Z, R^3, R^4 and X are as hereinbefore defined, and R^{2c} is hydrogen, cyano, nitro, halogen, N_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONR^{13}R^{14}$, COR^{15}, SO_2R^{16}, methylenedioxy, $NHCOR^{17}$ or heterocyclyl; wherein R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are as defined above, or a pharmaceutically acceptable salt thereof; or a solvate thereof.

In another aspect the present invention provides a compound of formula (Ia) wherein Z and R^{2c} are independently selected from the group consisting of: hydrogen,

$C(O)_2CH_3$, iodo, N_3, bromo, methyl, $C(O)_2CH_2CH_3$, cyano and methoxy; provided that Z and R^{2c} are not both hydrogen or methyl.

In yet another aspect the present invention provides a compound of formula (Ia) wherein R^3 is methyl; R^4 is $C(O)CH_3$; and X is NH; and: Z and R^{2c} are both CO_2CH_3; or Z is iodo and R^{2c} is hydrogen; or Z and R^{2c} are both iodo; or Z and R^{2c} are both N_3; or Z and R^{2c} are both bromo; Z and R^{2c} are both $CO_2CH_2CH_3$; or Z is hydrogen and R^{2c} is cyano; or Z is methoxy and R^{2c} is CO_2CH_3.

In a further aspect the present invention provides a compound of formula (Ib):



(Ib)

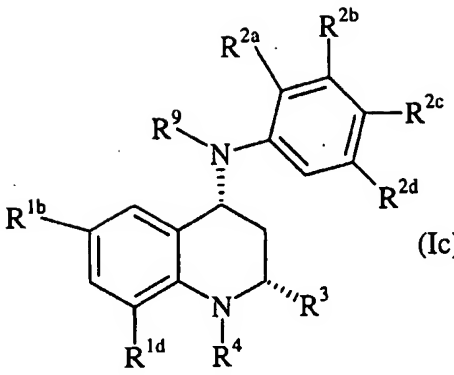
wherein R^2, R^3, R^4, X, Y and Z are as hereinbefore defined, or a pharmaceutically acceptable salt thereof; or a solvate thereof.

In a further aspect the present invention provides a compound of formula (I) wherein the relative configuration of the 2- and 4-position stereocentres is Z with the absolute configuration as depicted in formula (Ib). In a still further aspect the present invention provides a compound of formula (Ib) having an absolute configuration (2S, 4R) and wherein X is NH, R^3 is methyl, R^4 is $COCH_3$ and W, Y, Z and R^2 are as defined above.

In another aspect of the present invention W and Y are both hydrogen and Z is hydrogen, $C(O)_2CH_3$, iodo, N_3, bromo, methyl, $C(O)_2CH_2CH_3$, cyano or methoxy.

In a further aspect of the present invention R^2 is phenyl para-substituted by $C(O)_2CH_3$, iodo, N_3, bromo, methyl, $C(O)_2CH_2CH_3$, cyano or methoxy.

In a further aspect the present invention provides a compound of formula (Ic) wherein the substituent R^3 is cis to the substituted amine group at the 4 position of the tetrahydroquinoline:



(Ic)

wherein R^3, R^4 and R^9 are as hereinbefore defined;

R^{1b} is H, halogen, N_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), COC_{1-6} alkyl, SO_2Me or morpholin-4-yl;

R^{1d} is H or Me;

R^{2a} is H, halogen, C_{1-6} alkyl, C_{1-6} alkoxy or $CONH_2$;

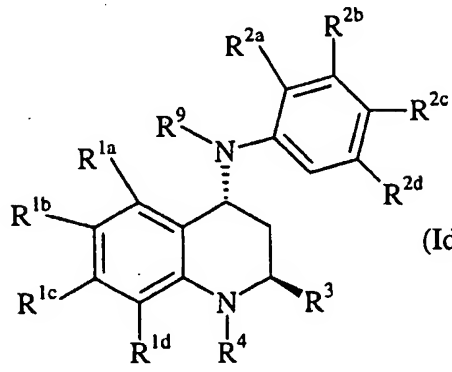
R^{2b} is H, halogen, C_{1-6} alkyl, or methylenedioxy;

R^{2c} is H, cyano, halogen, N_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONH_2$, COC_{1-6} alkyl, SO_2Me, methylenedioxy, NHCOMe or heterocyclyl; and

R^{2d} is H, C_{1-6} alkyl, or halogen,

or a pharmaceutically acceptable salt thereof; or a solvate thereof.

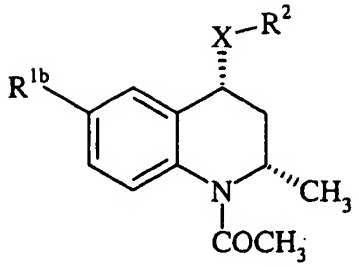
In a still further aspect the present invention provides a compound of formula (Id):



(Id)

wherein wherein R^{1b}, R^{1d}, R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^3, R^4 and R^9 are as hereinbefore defined; R^{1a} is H or C_{1-6} alkyl; and R^{1c} is H or C_{1-6} alkyl; or a pharmaceutically acceptable salt thereof; or a solvate thereof.

In another aspect the present invention provides a compound of formula (Ie):



(Ie)

wherein R^{1b} is H, Cl or CH_3; X is NH, S, or CH_2; and R^2 is pyrazin-2-yl or phenyl; or a pharmaceutically acceptable salt thereof; or a solvate thereof.

Compounds of formulae (Ia), (Ib), (Ic), (Id) and (Ie) are sub-groups of compounds of formula (I).

The following Tables provide examples of compounds of the invention. Table I illustrates compounds of formula (Ic); Table II illustrates compounds of formula (Id); and Table III illustrates compounds of formula (Ie).

TABLE I

Compound	R^{1b}	R^{1d}	R^{2a}	R^{2b}	R^{2c}	R^{2d}	R^3	R^4	R^9
1	H	H	H	H	H	H	Me	COMe	H
2	OMe	H	H	H	OMe	H	Me	COMe	H
3	Cl	H	H	H	Cl	H	Me	COMe	H
4	iso-Pr	H	H	H	iso-Pr	H	Me	COMe	H
5	I	H	H	H	I	H	Me	COMe	H
6	Br	H	H	H	Br	H	Me	COMe	H
7	F	H	H	H	F	H	Me	COMe	H
8	H	H	H	H	H	H	Me	COMe	COMe
9	Me	H	H	H	Me	H	Me	COMe	H
10	Et	H	H	H	Et	H	Me	COMe	H
11	cyclohexyl	H	H	H	cyclohexyl	H	Me	COMe	H
12	n-Bu	H	H	H	n-Bu	H	Me	COMe	H
13	SMe	H	H	H	SMe	H	Me	COMe	H
14	OMe	H	H	H	OMe	H	Me	COMe	COMe
15	Me	H	H	H	Me	H	Me	COEt	H
16	N_3	H	H	H	N_3	H	Me	COMe	H
17	CO_2H	H	H	H	CO_2H	H	Me	COMe	H

18	CO_2Me	H	H	H	CO_2Me	H	Me	COMe	H
19	H	H	Cl	H	H	H	Me	COMe	H
20	H	H	H	Cl	H	H	Me	COMe	H
21	H	H	H	H	Cl	H	Me	COMe	H
22	H	H	H	H	Br	H	Me	COMe	H
23	H	H	H	H	I	H	Me	COMe	H
24	H	H	OMe	H	H	H	Me	COMe	H
25	H	H	H	H	OMe	H	Me	COMe	H
26	H	H	H	Me	H	H	Me	COMe	H
27	H	H	H	H	Me	H	Me	COMe	H
28	H	H	Cl	H	Me	H	Me	COMe	H
29	H	H	Me	H	Cl	H	Me	COMe	H
30	H	H	Cl	Cl	H	H	Me	COMe	H
31	H	H	Cl	H	Cl	H	Me	COMe	H
32	H	H	Cl	H	H	Cl	Me	COMe	H
33	H	H	H	Cl	Cl	H	Me	COMe	H
34	H	H	H	Cl	H	Cl	Me	COMe	H
35	H	H	H	H	cyclohexyl	H	Me	COMe	H
36	H	H	H	H	CN	H	Me	COMe	H

					Methylenedioxy					
37	H	H	H	H	Me	H	Me	COMe	H	
38	Cl	H	H	H	Morpholin-4-yl	H	Me	COMe	H	
39	Cl	H	H	H	OMe	H	Me	COMe	H	
40	Me	H	H	H	OMe	H	Me	COMe	H	
41	Cl	H	H	H	CO_2Et	H	Me	COMe	H	
42	CO_2Et	H	H	H	CN	H	Et	COMe	H	
43	H	H	H	H	CO_2CHMe_2	H	Me	COMe	H	
44	CO_2CHMe_2	H	H	H	Cl	H	Me	COMe	H	
45	OMe	H	H	H	Me	H	Me	COMe	H	
46	OMe	H	H	H	Benzoyl	H	Me	COMe	H	
47	OMe	H	H	H	CO_2Me	H	Me	COMe	H	
48	Cl	H	H	H	COMe	H	Me	COMe	H	
49	OMe	H	H	H	$CONH_2$	H	Me	COMe	H	
50	OMe	H	H	H	CN	H	Me	COMe	H	
51	OMe	H	H	H	CO_2Me	H	Me	COMe	H	
52	OMe	H	H	H	CN	H	Me	COMe	H	
53	H	Me	H	H	Morpholin-4-yl	H	Me	COMe	H	
54	OMe	H	H	H	H	H	Me	COMe	H	
55	Cl	H	H	$CONH_2$	H					

56	H	H	H	H	$CONH_2$	H	Me	COMe	H
57	Me	H	H	H	CN	H	Me	COMe	H
58	Me	H	H	H	Morpholin-4-yl	H	Me	COMe	H
59	H	H	$CONH_2$	H	H	H	Me	COMe	H
60	H	H	H	H	NHCOMe	H	Me	COMe	H
61	Cl	H	H	H	NHCOMe	H	Me	COMe	H
62	H	H	H	H	CO_2Me	H	Me	COMe	H
63	OMe	H	H	H	NHCOMe	H	Me	COMe	H
64	OMe	H	H	H	SO_2Me	H	Me	COMe	H
65	Br	H	H	H	Benzoyl	H	Me	COMe	H
66	Morpholin-4-yl	H	H	H	OMe	H	Me	COMe	H
67	Morpholin-4-yl	H	H	H	CN	H	Me	COMe	H
68	Morpholin-4-yl	H	H	H	H	H	Me	COMe	H
69	H	H	H	H	CO_2Me	H	Et	COMe	H
70	H	H	H	H	H	H	Phenyl	COMe	H
71	H	H	H	H	CN	H	Me	COMe	H
72	SMe	H	H	H	H	H	Me	COMe	H
73	SO_2Me	H	H	H	H	H	Me	COMe	H
74	I	H	H	H	H	H	Me	COMe	H

75	Br	H	H	H	H	H	Me	COMe	H

TABLE II

Compound	R^{1a}	R^{1b}	R^{1c}	R^{1d}	R^{2a}	R^{2b}	R^{2c}	R^{2d}	R^3	R^4	R^9
1	H	H	H	H	H	H	H	H	Me	COMe	H
2	H	OMe	H	H	H	H	OMe	H	Me	COMe	COMe
3	H	H	H	H	H	H	H	H	Me	COMe	COMe
4	H	Cl	H	H	H	H	Cl	H	Me	COMe	COMe
5	Me	H	Me	H	H	Me	H	Me	Me	COMe	COMe
6	H	iso-Pr	H	H	H	H	iso-Pr	H	Me	COMe	COMe
7	H	I	H	H	H	H	I	H	Me	COMe	COMe
8	H	F	H	H	H	H	F	H	Me	COMe	COMe
9	H	Br	H	H	H	H	Br	H	Me	COMe	COMe
10	H	Me	H	H	H	H	Me	H	Me	COMe	COMe
11	H	Et	H	H	H	H	Et	H	Me	COMe	COMe
12	H	Cyclohexyl	H	H	H	H	Cyclohexyl	H	Me	COMe	COMe
13	H	n-Bu	H	H	H	H	n-Bu	H	Me	COMe	COMe
14	H	SMe	H	H	H	H	SMe	H	Me	COMe	COMe

15	H	Me	H	H	H	H	Me	H	Me	COPh	H
16	H	Me	H	H	H	H	Me	H	Me	COEt	H
17	H	N_3	H	H	H	H	N_3	H	Me	COMe	COMe
18	H	CO_2Me	H	H	H	H	CO_2Me	H	Me	COMe	H
19	H	COMe	H	H	H	H	COMe	H	Me	COMe	COMe
20	H	N_3	H	H	H	H	N_3	H	Me	COMe	H
21	H	H	H	H	Cl	H	H	H	Me	COMe	H
22	H	H	H	H	H	Cl	H	H	Me	COMe	H
23	H	H	H	H	H	H	Cl	H	Me	COMe	H
24	H	H	H	H	H	H	Br	H	Me	COMe	H
25	H	H	H	H	H	H	I	H	Me	COMe	H
26	H	H	H	H	OMe	H	H	H	Me	COMe	H
27	H	H	H	H	H	H	OMe	H	Me	COMe	H
28	H	H	H	H	H	Me	H	H	Me	COMe	H
29	H	H	H	H	H	H	Me	H	Me	COMe	H
30	H	H	H	H	Cl	H	Me	H	Me	COMe	H
31	H	H	H	H	Me	H	Cl	H	Me	COMe	H
32	H	H	H	H	Cl	Cl	H	H	Me	COMe	H
33	H	H	H	H	Cl	H	Cl	H	Me	COMe	H

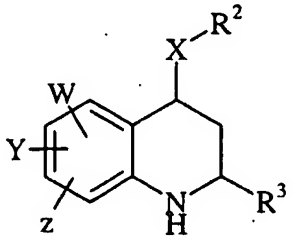
34	H	H	H	H	Cl	H	H	Cl	Me	COMe	H
35	H	H	H	H	H	Cl	Cl	H	Me	COMe	H
36	H	H	H	H	H	Cl	H	Cl	Me	COMe	H
37	H	H	H	H	H	H	Cyclohexyl	H	Me	COMe	H
38	H	H	H	H	H	H	CN	H	Me	COMe	H
39	H	H	H	H	H	Methylenedioxy		H	Me	COMe	H
40	H	Cl	H	H	H	H	Me	H	Me	COMe	H
41	H	Cl	H	H	H	H	Morpholin-4-yl	H	Me	COMe	H
42	H	Me	H	H	H	H	OMe	H	Me	COMe	H
43	H	Cl	H	H	H	H	OMe	H	Me	COMe	H
44	H	H	H	H	H	H	CO_2Me	H	Et	COMe	H
45	H	H	H	H	H	H	CN	H	Et	COMe	H
46	H	CO_2CHMe_2	H	H	H	H	CO_2CHMe_2	H	Me	COMe	H
47	H	OMe	H	H	H	H	Benzoyl	H	Me	COMe	H
48	H	Cl	H	H	H	H	CO_2Me	H	Me	COMe	H
49	H	OMe	H	H	H	H	$CONH_2$	H	Me	COMe	H
50	H	OMe	H	H	H	H	CN	H	Me	COMe	H
51	H	OMe	H	H	H	H	CO_2Me	H	Me	COMe	H
52	H	H	H	Me	H	H	CN	H	Me	COMe	H

53	H	OMe	H	H	H	H	Morpholin-4-yl	H	Me	COMe	H
54	H	Cl	H	H	$CONH_2$	H	H	H	Me	COMe	H
55	H	Cl	H	H	H	H	$CONH_2$	H	Me	COMe	H
56	H	H	H	H	H	H	$CONH_2$	H	Me	COMe	H
57	H	Me	H	H	H	H	CN	H	Me	COMe	H
58	H	Me	H	H	H	H	Morpholin-4-yl	H	Me	COMe	H
59	H	H	H	H	$CONH_2$	H	H	H	Me	COMe	H
60	H	H	H	H	H	H	NHCOMe	H	Me	COMe	H
61	H	H	H	H	H	H	CO_2Me	H	Me	COMe	H
62	H	OMe	H	H	H	H	NHCOMe	H	Me	COMe	H
63	H	Morpholin-4-yl	H	H	H	H	CN	H	Me	COMe	H
64	H	Morpholin-4-yl	H	H	H	H	H	H	Me	COMe	H
65	H	SMe	H	H	H	H	H	H	Me	COMe	H

TABLE III

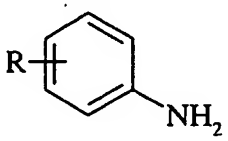
Compound No.	R^{1b}	X	R^2
1	H	NH	Pyrazin-2-yl
2	Cl	NH	Pyrazin-2-yl
3	H	NH	Pyridin-4-yl
4	CH_3	S	Phenyl
5	H	CH_2	Phenyl

According to the invention there is further provided a process for the preparation of a compound of formula (I) which comprises reacting a compound of formula (II):



(II)

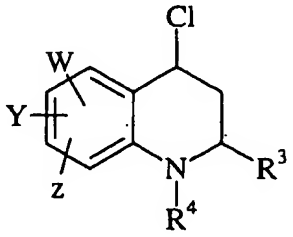
with a suitable acid anhydride in the presence of a suitable base (such as pyridine) at a suitable temperature (such as room temperature). A compound of formula (II), wherein W and Y are both hydrogen, Z is at the 6-position, R^2 is para-substituted phenyl where its substituent is the same as Z, and R^3 is methyl, can be prepared by a Doebner-von Miller type reaction, that is by reacting an aniline of formula (III):



(III)

wherein R is Z or the substituent on R^2, with acetaldehyde in a suitable solvent (for example ethanol/water) at a suitable temperature (such as room temperature).

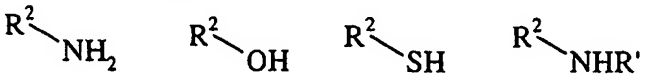
Alternatively, a compound of formula (I) can be prepared by reacting a compound of formula (IV):



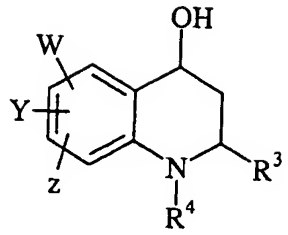
(IV)

with a compound of formula (V):

(V)

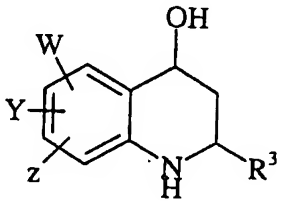


wherein R' is alkyl, in a suitable solvent (such as acetonitrile) with a suitable base and at a suitable temperature (such as reflux). A compound of formula (IV) can be prepared by chlorinating a compound of formula (VI):



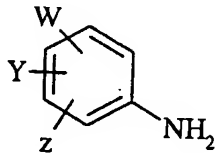
(VI)

with a suitable chlorinating reagent (such as thionyl chloride) in a suitable solvent (such as dichloromethane). A compound of formula (VI) can be prepared by acylating a compound of formula (VII):



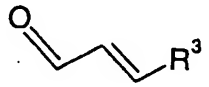
(VII)

(for example with an acid anhydride $(R^4)_2O$) in a suitable solvent (such as dichloromethane). A compound of formula (VII) can be prepared by reacting an aniline of formula (VIII):



(VIII)

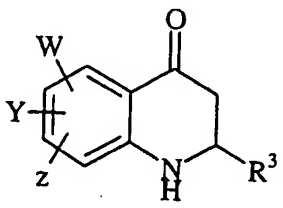
with a compound of formula (IX):



(IX)

in the presence of a suitable acid and solvent (such as aqueous 5% hydrochloric acid).

Alternatively, a compound of formula (VI) can be prepared by acetylation (for example with an acid anhydride $(R^4)_2O$) and subsequent reduction of a compound of formula (X):



(X)

Alternatively compounds of formula (I) can be prepared as shown in Scheme 1 below. Both racemic and enantioselective synthesis can be prepared by this route.

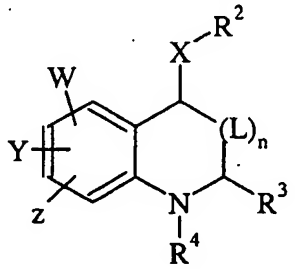
Compounds of formula (Ib) can be prepared as shown in Scheme 2 below.

Compounds of formulae (III) and (IX) are commercially available or can be prepared using or adapting literature methods.

In another aspect the present invention provides processes for the preparation of a compound of formula (I), (Ia), (Ib), (Ic), (Id) or (Ie).

Compounds of the invention are useful because they demonstrate pharmacological activity. In particular they demonstrate activity as modulators of the STAT6 signal pathway. The compounds of the invention, being modulators of the STAT6 pathway, can be used to treat atopic dermatitis, urticaria, allergic asthma, allergic rhinitis, food allergies, allergic conjunctivitis, hayfever, bullous pemphigoid, industrial sensitisation or chronic rejection of transplants, or COPD.

The present invention also provides a compound of formula (I):



(I)

wherein:

L is CH_2, O or S;

n is 0 or 1;

W, Y and Z are, independently hydrogen, cyano, nitro, halogen, N_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONR^5R^6$, COR^{10}, SO_2R^{12}, methylenedioxy, $NHCOR^{11}$ or heterocyclyl;

R^2 is aryl or heteroaryl optionally substituted by cyano, nitro, halogen, N_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONR^{13}R^{14}$, COR^{15}, SO_2R^{16}, methylenedioxy, $NHCOR^{17}$ or heterocyclyl;

R^3 is C_{1-4} alkyl or C_{1-4} haloalkyl;

R^4 is $CO(C_{1-4}$ alkyl) or $CO(C_{1-4}$ haloalkyl);

X is O, S, SO, SO_2, CR^7R^8 or NR^9;

R^5, R^6, R^7, R^8, R^{13} and R^{14} are, independently, hydrogen or C_{1-6} alkyl;

R^9 is hydrogen, C_{1-6} alkyl or $CO(C_{1-4}$ alkyl);

R^{10}, R^{11}, R^{12}, R^{15}, R^{16} and R^{17} are, independently, C_{1-6} alkyl or phenyl;

or a pharmaceutically acceptable salt thereof; or a solvate thereof, for use in medical therapy. The term 'medical therapy' as used herein is intended to include prophylactic, diagnostic and therapeutic regimens carried out in vivo or ex vivo on humans or other mammals.

According to the invention there is further provided the use of a compound of invention of formula (I) as defined anywhere above, (Ia), (Ib), (Ic), (Id) or (Ie), or a pharmaceutically acceptable salt thereof; or solvate thereof, in the manufacture of a medicament for use in therapy (such as in the modulation of the STAT6 signal pathway; for example in the treatment of atopic dermatitis, urticaria, allergic asthma, allergic rhinitis, a food allergy, allergic conjunctivitis, hayfever, bullous pemphigoid, industrial sensitization, chronic rejection of transplants or COPD; especially allergic asthma, or allergic rhinitis, or COPD) in a mammal (such as a human).

A method of treating STAT6 mediated disease state {such as atopic dermatitis, urticaria, allergic asthma, allergic rhinitis, a food allergy, allergic conjunctivitis, hayfever, bullous pemphigoid, industrial sensitization, chronic rejection of transplants or COPD; especially allergic asthma, or allergic rhinitis, or COPD} in a mammal (such as a human) which comprises administering to a mammal in need of such treatment an effective amount of a compound of formula (I), (Ia), (Ib), (Ic), (Id) or (Ie), or a pharmaceutically acceptable salt thereof; or a solvate thereof.

The dose of the compound to be administered will depend on the relevant indication, the age, weight and sex of the patient and may be determined by a physician. The dosage will preferably be in the range of from 0.01 mg/kg to 10 mg/kg.

The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aerosols or dry powder formulations, for example formulations in the inhaler device known as the TURBUHALER®; or systemically, for example by oral administration in the form of a tablet, pill, capsule, syrup, powder or granule, or by parenteral administration, for example, in the form of sterile

parenteral solution or suspension, or by rectal administration, for example in the form of suppositories.

The compounds of the invention may be administered on their own or as a pharmaceutical comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant and/or carrier. Particularly preferred are compositions not containing material capable of causing an adverse, such as an allergic, reaction. Also provided by the present invention is a pharmaceutical composition comprising a compound according to the present invention, as active ingredient, together with a pharmaceutically acceptable adjuvant, diluent or carrier.

Dry powder formulations and pressurized HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation the compound is desirably finely divided. The finely divided compound preferably has a mass median diameter of less than 10μm, and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C_8-C_{20} fatty acid or salt thereof, (such as oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.

The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound with a carrier substance, for example a mono-, di- or polysaccharide, a sugar alcohol, or another polyol. Suitable carriers are sugars, for example lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose or mannitol; and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatin capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, for example that known as the TURBUHALER® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound, with or without a carrier substance, is delivered to the patient.

For oral administration the active compound may be admixed with an adjuvant or a carrier, for example lactose, saccharose, sorbitol or mannitol; a starch, for example potato starch, corn starch or amylopectin; a cellulose derivative; a binder, for example gelatin or polyvinylpyrrolidone, and/or a lubricant, for example magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, or the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain for example gum arabic, gelatin, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatin capsules, the compound may be admixed with for example a vegetable oil or polyethylene glycol. Hard gelatin capsules may contain granules of the compound using either the above mentioned excipients for tablets. Also liquid or semisolid formulations of the drug may be filled into hard gelatin capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain coloring agents, flavoring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The compounds of the invention may be administered in conjunction with other compounds used for the treatment of the above conditions.

The following Examples illustrate the invention. Throughout the Examples all reactions were performed in dried glassware in an argon or nitrogen atmosphere at room temperature, unless otherwise noted. All solvents and reagents were used as received.

^{1}H-NMR spectra were recorded at 400MHz. The residual solvent peak, usually chloroform (δ_H 7.27 ppm) was used as internal shift reference. Analytical HPLC was run on a Hewlett Packard LC-MS 1100, using a C-18 reversed phase column and eluting with the following general system: acetonitrile:0.1M NH_4OAc (20:80 to 90:10 gradient)

Preparative LC was run on a Kromasil KR-100-10-C18 column (250x20 mm), using different proportions of acetonitrile:water containing 2.0% HOAc or acetonitrile:0.1M NH_4OAc, as eluent. Chiral separations was performed on Chiralpak AD

columns using different proportions of hexane, 2-propanol, methanol and diethylamine. Flash chromatography was performed on silica (Merck 40-63 μm) with the eluents indicated in the specific Examples.

EXAMPLE 1

This Example illustrates the preparation of *cis*-1-Acetyl-6-ethyl-*N*-(4-ethylphenyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinamine (Compound No. 10 Table I)

Step 1: *cis* -6-Ethyl-*N*-(4-ethylphenyl)-2-methyl-1,2,3,4-tetrahydro-4-quinolinamine

Acetaldehyde (0.77g, 17.4 mmol) was added to an ice-cooled solution of p-ethylaniline (0.71g, 5.8 mmol) in aqueous ethanol (20ml, 60%). After stirring at room temperature for 24 hours the solvents were evaporated. The crude product was purified on silica (ethyl acetate:heptane 1:4) and preparative HPLC to yield the cis:trans isomers in a 1:2 ratio to provide the sub-titled product (0.65 mmol). (The corresponding trans-isomer was also isolated 1.3 mmol.)

Step 2: *cis* -1-Acetyl-6-ethyl-*N*-(4-ethylphenyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinamine.

The compound of Step 1 (59mg, 0.20 mmol) was dissolved in pyridine (1ml) and acetic anhydride (2.0 mmol) was added. After stirring at room temperature for 20 hours the solvent was evaporated and the crude product was purified on silica (ethyl acetate : heptane 1:2). The title compound was obtained as a colorless oil (0.12 mmol).

^{1}H NMR $CDCl_3$: δ 7.23 (1H, s); 7.16-7.00 (4H, m); 6.63 (2H, d); 4.90 (1H, br s); 4.24-4.14 (1H, m); 3.82-3.68 (1H, m); 2.70-2.52 (5H, m); 2.20 (3H, s); 1.38-1.15 (10H, m).

EXAMPLE 2

This Example illustrates the preparation of 4-{[(2S*,4R*)-1-acetyl-2-methyl-1,2,3,4-tetrahydro-4-quinolinyl]amino}benzonitrile (Compound No. 36 of Table I) and the preparation of 4-[{(2R*,4R*)1-acetyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl}amino]-benzonitrile. (Compound No. 45 Table II).

Step 1: 1-(4-Hydroxy-2-methyl-3,4-dihydro-2*H*-quinolin-1-yl)-ethanone.

A solution of 1,2,3,4-tetrahydro-2-methyl-4-quinolinol (5.9g, 36.4 mmol) and acetic anhydride (37.1g, 364 mmol) in dichloromethane (100ml) was stirred for one hour. The

solvents were evaporated and the crude product was purified on silica (ethyl acetate : heptane 1:1) to obtain the sub-titled product (33.5 mmol).

Step 2:

1-(4-Hydroxy-2-methyl-3,4-dihydro-2*H*-quinolin-1-yl)-ethanone (3.1g, 15 mmol) was dissolved in dry dichloromethane (50 ml). Thionyl chloride (1.96g, 16.5 mmol) was added at -10°C and the reaction mixture was stirred vigorously for about 30 minutes. The reaction mixture was filtered through a short plug of silica and eluted with dichloromethane. The solvents were removed by reduced pressure affording a yellowish oil (2.15g).

The oil was dissolved in dry acetonitrile (60ml) and 4-aminobensonitrile (3.54g, 30 mmol) was added. The flask was sealed and heated at 80°C for 12 h. The solvent was removed at reduced pressure and the crude product was purified on silica using ethyl acetate : heptane 1:1 as eluent, affording the product (4.6 mmol). The product was further purified on preparative HPLC to yield the cis/trans diastereomers in a 2:3 ratio (1.8 mmol of the cis compound and 2.7 mmol of the trans compound) as white solids after lyophilisation. The enantiomers were resolved according to the general procedures.

Compound No. 36 of Table I: $[\alpha]_D^{20} = 171°$ (c = 0.28, CH_2Cl_2); ^1H NMR $CDCl_3$: δ 7.46 (2H, d); 7.32 (1H, dt); 7.24-7.14 (3H, m); 6.63 (2H, d); 5.00-4.88 (1H, m); 4.42 (1H, br d); 4.31-4.23 (1H, m); 2.73-2.63 (1H, m); 2.20 (3H, s); 1.34 (1H, q); 1.17 (3H, d).

Compound No. 45 Table II: $[\alpha]_D^{20} = 56°$ (c = 0.53, CH_2Cl_2); ^1H NMR $CDCl_3$: δ 7.45-7.18 (6H, m); 6.62 (2H, d); 5.0-4.85 (1H, m); 4.62 (1H, t); 4.40 (1H, d); 2.58-2.49 (1H, m); 2.18 (3H, s); 1.82-1.75 (1H, m); 1.20 (3H, d).

EXAMPLE 3

This Example illustrates the preparation of (2S,4R)-1-Acetyl-2-methyl-*N*-phenyl-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 1 of Table I).

Step 1: 1-[(2S)-2-methyl-4-(phenylimino)-3,4-dihydro-1(2*H*)-quinolinyl]-1-ethanone.

A solution of (2S)-1-acetyl-2-methyl-2,3-dihydro-4(1*H*)-quinolinone (20mg, 0.098 mmol; preparation see Tetrahedron: Asymmetry (1998), 9(7), 1137-1142), aniline (36µl, 0.394mmol) and a catalytic amount of p-toluene sulfonic acid monohydrate was refluxed

overnight in toluene (4ml) containing molcular sieve 3Å (0.9g). The resulting mixture was filtered, concentrated and purified on silica (ethyl acetate:heptane 1:2) to obtain the sub-titled product (22.8mg, 0.082 mmol).

Step 2: (2S, 4R)-1-Acetyl-2-methyl-*N*-phenyl-1,2,3,4-tetrahydro-4-quinolinamine.

A solution of the product of Step 2 (13mg, 0,047 mmol) in ethyl acetate (5ml) was hydrogenated for four hours at 1 atmosphere in the presence of palladium on charcoal (15mg, 10%). The mixture was filtered and the residue was concentrated and purified on silica (ethyl acetate : heptane 1:2). The title compound was obtained as a colorless oil (0.025 mmol). $[\alpha]_D^{20} = 236°$ (c 0.53, CH_2Cl_2).

^{1}H NMR $CDCl_3$: δ 7.37-7.11 (6H, m); 6.77 (1H, t); 6.66 (2H, d); 4.92 (1H, br d); 4.22 (1H, dd); 4.14-3.60 (1H, br s); 2.70-2.61 (1H, m); 2.18 (3H, s); 1.35-1.22 (1H, m); 1.17 (3H, d).

EXAMPLE 4

This Example illustrates the preparation of *cis*-1-acetyl-2,6-dimethyl-1,2,3,4-tetrahydro-4-quinolinyl phenyl sulfide (Compound No. 4 of Table III).

To a mixture of 1-acetyl-4-chloro-1,2,3,4-tetrahydro-2,6-dimethyl- quinoline (200mg, 0.84 mmol) and sodium hydride (20mg) in THF (2ml) was added a solution of benzenethiol (66µl, 1.2 mmol) in THF (1ml). The mixture was stirred for 16 hrs. Water was added and the product was extracted with ethyl acetate. The crude product was purified on silica (ethyl acetate/heptane) and with preparative HPLC to yield the sub-title product (0.18 mmol) together with its trans isomer (0.12 mmol).

^{1}H NMR $CDCl_3$: δ 7.42-7.40 (6H, m); 7.21 (1H, d); 7.04-6.95 (1H, d); 4.81 (1H, s); 4.03 (1H, dd); 2.62 (1H, m); 2.39 (3H, s); 2.16 (3H, s); 1.41-1.32 (1H, m); 1.12 (3H, d).

EXAMPLE 5

This Example illustrates the preparation of *cis*-1-Acetyl-2-methyl-4-(phenylmethyl)-1,2,3,4-tetrahydroquinoline (Compound No. 5 of Table III).

To a solution of (2*S*)-1-acetyl-2-methyl-2,3-dihydro-4(1*H*)-quinolinone (100mg, 0.49 mmol) in dry toluene (5ml) was added benzyl magnesium chloride (0.98 mmol, 1.3M in THF). The solution was refluxed for 5 hrs and then quenched with aqueous sulfuric acid.

The aqueous phase was extracted with ether, the solvents were evaporated and the crude product was purified on silica (ethyl acetate/heptane) to obtain a yellow oil (79mg). The oil was dissolved in THF (3ml) and aqueous sulfuric (2M, 10ml) acid was added. The solution was stirred over night, extracted with ether and the solvents were evaporated to a yellow oil (40mg). The crude product was dissolved in ethyl acetate (10mg) and was hydrogenated for 16 hours at 1 atmosphere in the presence of palladium on charcoal (100mg, 10%). The mixture was filtered and the residue was concentrated and purified with preparative HPLC. The title compound was obtained as colorless oil (16mg, 0.20 mmol).
^{1}H NMR $CDCl_3$: δ 7.39-7.21 (8H, m); 7.17 (1H, br d); 4.87 (1H, br s); 3.48 (1H, dd); 2.79-2.65 (1H, m); 3.62 (1H, dd); 2.29-2.22 (1H, m); 2.17 (3H, s); 1.02 (3H, d); 0.90-0.81 (1H, m).

Proton NMR data are provided for compounds of formula (I).

cis-1-Acetyl-1,2,3,4-tetrahydro-6-methoxy-*N*-(4-methoxyphenyl)-2-methyl-4-quinolinamine (Compound No. 2 Table I).
^{1}H NMR $CDCl_3$: δ 7.03 (1H, br d); 6.92 (1H, d); 6.78 (3H, m); 6.61 (2H, m); 4.90 (1H, br s); 4.09 (1H, br d); 3.76 (3H, s); 3.73 (3H, s); 3.50 (1H, br s); 2.66-2.57 (1H, m); 2.14 (3H, s); 1.22-1.05 (4H, m).

cis -1-Acetyl-6-chloro-*N*-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinamine (Compound No. 3 Table I).
^{1}H NMR $CDCl_3$: δ 7.29-7.21 (1H, m); 7.19-7.03 (4H, m); 6.54 (2H, d); 4.86 (1H, br s); 4.14-4.06 (1H, m); 3.85 (1H, d); 2.67-2.59 (1H, m); 2.17 (3H, s); 1.32-1.19 (1H, m); 1.14 (3H, d).

cis -1-Acetyl-1,2,3,4-tetrahydro-2-methyl-6-(1-methylethyl)-*N*-[4-(1-methylethyl)phenyl]-4-quinolinamine (Compound No. 4 Table I).
^{1}H NMR $CDCl_3$: δ 7.24 (1H, br s); 7.16-7.03 (4H, m); 6.64 (2H, d); 4.88 (1H, br d); 4.20 (1H, br d); 3.68 (1H, br s); 2.96-2.78 (2H, m); 2.70-2.60 (1H, m); 2.19 (3H, s); 1.33-1.18 (13H, m); 1.16 (3H, d).

cis -1-Acetyl-1,2,3,4-tetrahydro-6-iodo-*N*-(4-iodophenyl)-2-methyl-4-quinolinamine (Compound No. 5 Table I).

^{1}H NMR $CDCl_3$: δ 7.64 (1H, dd); 7.58 (1H, s); 7.46 (2H, d); 6.91 (1H, br d); 6.42 (2H, d); 4.86 (1H, br d); 4.16-4.07 (1H, m); 3.80 (1H, d); 2.68-2.58 (1H, m); 2.18 (3H, s); 1.35-1.20 (1H, m); 1.16 (3H, d).

(2S*,4R*)-1-Acetyl-6-bromo-*N*-(4-bromophenyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinamine (Compound No. 6 Table I). $[\alpha]_D^{20} = 267°$ (c = 0.004, CH_2Cl_2).

^{1}H NMR $CDCl_3$: δ 7.44-7.36 (2H, m); 7.27 (2H, d); 7.02 (1H, br d); 6.49 (2H, d); 4.85 (1H, br s); 4.15-4.05 (1H, m); 3.87 (1H, d); 2.67-2.58 (1H, m); 2.17 (3H, s); 1.34-1.18 (1H, m); 1.14 (3H, d).

cis -1-Acetyl-6-fluoro-*N*-(4-fluorophenyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinamine (Compound No. 7 Table I).

^{1}H NMR $CDCl_3$: δ 7.16-6.86 (5H, m); 6.60-6.53 (2H, m); 4.91 (1H, br s); 4.14-4.04 (1H, m); 3.75 (1H, d); 2.70-2.60 (1H, m); 2.17 (3H, s); 1.34-1.18 (1H, m); 1.14 (3H, d).

(2S*,4R*)-1-Acetyl-1,2,3,4-tetrahydro-2,6-dimethyl-*N*-(4-methylphenyl)- 4-quinolinamine (Compound No. 9 Table I). $[\alpha]_D^{20} = 36°$ (c = 0.28, CH_2Cl_2).

^{1}H NMR $CDCl_3$: δ 7.17 (1H, s); 7.12-6.98 (4H, m); 6.58 (2H, d); 4.89 (1H, br s); 4.15 (1H, br d); 3.66 (1H, br s); 2.68-2.58 (1H, m); 2.32 (3H, s); 2.27 (3H, s); 2.18 (3H, s); 1.36-1.18 (1H, m); 1.14 (3H, d).

cis -1-Acetyl-6-cyclohexyl-*N*-(4-cyclohexylphenyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinamine (Compound No. 11 Table I).

^{1}H NMR $CDCl_3$: δ 7.21 (1H, s); 7.12-6.98 (4H, m); 6.61 (2H, d); 4.85 (1H, br s); 4.22-4.11 (1H, m); 3.62 (1H, d); 2.68-2.57 (1H, m); 2.54-2.34 (2H, m); 2.17 (3H, s); 1.94-1.12 (24H, m).

cis -1-Acetyl-6-butyl-*N*-(4-butylphenyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinamine (Compound No. 12 Table I).

^{1}H NMR $CDCl_3$: δ 7.18 (1H, s); 7.12-6.97 (4H, m); 6.61 (2H, d); 4.88 (1H, br s); 4.22-4.12 (1H, m); 3.68 (1H, br d); 2.70-2.46 (5H, m); 2.18 (3H, s); 1.66-1.49 (4H, m); 1.44-1.12 (8H, m); 1.02-0.86 (6H, m).

cis -1-Acetyl-1,2,3,4-tetrahydro-2-methyl-6-(methylthio)-*N*-[4-(methylthio)phenyl]- 4-quinolinamine (Compound No. 13 Table I).

^{1}H NMR $CDCl_3$: δ 7.23-6.98 (5H, m); 7.57 (2H, d); 4.92-4.74 (1H, m); 4.18-4.10 (1H, m); 3.84 (1H, br d); 2.66-2.57 (1H, m); 2.40 (3H, s); 2.38 (3H, s); 2.15 (3H, s); 1.32-1.18 (1H, m); 1.13 (3H, d).

cis -1,2,3,4-Tetrahydro-2,6-dimethyl-*N*-(4-methylphenyl)-1-(1-oxopropyl)- 4-quinolinamine (Compound No. 15 Table I).

^{1}H NMR $CDCl_3$: δ 7.14 (1H, s); 7.09-6.97 (4H, m); 6.56 (2H, d); 4.96-4.82 (1H, m); 4.11 (1H, dd); 3.64 (1H, br s); 2.66-2.32 (3H, m); 2.31 (3H, s); 2.25 (3H, s); 1.34-1.08 (7H, m).

cis -1-Acetyl-6-azido-*N*-(4-azidophenyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinamine (Compound No. 16 Table I).

^{1}H NMR $CDCl_3$: δ 7.18-6.82 (5H, m); 6.61 (2H, d); 4.88 (1H, br s); 4.13 (1H, dd); 3.77 (1H, br s); 2.68-2.60 (1H, m); 2.16 (3H, s); 1.34-1.10 (4H, m).

cis -1-Acetyl-4-[(4-carboxyphenyl)amino]-1,2,3,4-tetrahydro-2-methyl-6-quinolinecarboxylic acid (Compound No. 17 Table I).

^{1}H NMR MeOD (two protons are obscured by the H_2O-signal): δ 7.96-7.74 (4H, m); 7.33 (1H, d); 6.68 (2H, d); 4.37 (1H, dd); 2.74-2.62 (1H, m); 2.24-2.13 (3H, m); 1.43-1.23 (1H, m); 1.17 (3H, d).

cis -1-Acetyl-1,2,3,4-tetrahydro-4-[[4-(methoxycarbonyl)phenyl]amino]-2-methyl- 6-quinolinecarboxylic acid methyl ester (Compound No. 18 Table I).

^{1}H NMR $CDCl_3$: δ 7.99 (1H, dd); 7.94-7.86 (3H, m); 7.28-7.20 (1H, m); 6.62 (2H, d); 4.94-4.82 (1H, m); 4.37-4.23 (2H, m); 3.85 (6H, s); 2.74-2.64 (1H, m); 2.22 (3H, s); 1.40-1.28 (1H, m); 1.18 (3H, d).

cis -1-Acetyl-*N*-(2-chlorophenyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinamine (Compound No. 19 Table I).

^{1}H NMR $CDCl_3$: δ 7.36-7.08 (6H, m); 6.70 (1H, dt); 6.61 (1H, d); 4.95 (1H, br d); 4.51 (1H, d); 4.31-4.22 (1H, m); 2.76-2.66 (1H, m); 2.20 (3H, s); 1.38 (1H, q); 1.19 (3H, d).

cis -1-Acetyl-*N*-(3-chlorophenyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinamine (Compound No. 20 Table I).

^{1}H NMR $CDCl_3$: δ 7.34-7.07 (5H, m); 6.76-6.70 (1H, m); 6.63 (1H, t); 6.52 (1H, dd); 5.00-4.85 (1H, m); 4.25-4.16 (1H, m); 3.91 (1H, d); 2.71-2.61 (1H, m); 2.20 (3H, s); 1.35-1.22 (1H, m); 1.17 (3H, d).

cis -1-Acetyl-*N*-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinamine (Compound No. 21 Table I).

^{1}H NMR $CDCl_3$: δ 7.35-7.07 (6H, m); 6.61-6.53 (2H, m); 5.00-4.84 (1H, m); 4.17 (1H, d); 3.86 (1H, br s); 2.71-2.60 (1H, m); 2.20 (3H, s); 1.35-1.22 (1H, m); 1.16 (3H, d).

cis -1-Acetyl-*N*-(4-bromophenyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinamine (Compound No. 22 Table I).

^{1}H NMR $CDCl_3$: δ 7.34-7.10 (5H, m); 6.89 (1H, br s); 6.53 (2H, d); 5.00-4.85 (1H, m); 4.17 (1H, dd); 2.71-2.60 (1H, m); 2.20 (3H, s); 1.34-1.22 (1H, m); 1.17 (3H, d).

cis -1-Acetyl -1,2,3,4-tetrahydro-*N*-(4-iodophenyl)-2-methyl-4-quinolinamine (Compound No. 23 Table I).

^{1}H NMR $CDCl_3$: δ 7.45 (2H, d); 7.34-7.10 (4H, m); 6.44 (2H, d); 4.99-4.85 (1H, m); 4.17 (1H, dd); 3.88 (1H, br s); 2.70-2.60 (1H, m); 2.19 (3H, s); 1.34-1.21 (1H, m); 1.16 (3H, d).

cis -1-Acetyl-1,2,3,4-tetrahydro-*N*-(2-methoxyphenyl)-2-methyl-4-quinolinamine (Compound No. 24 Table I).

^{1}H NMR $CDCl_3$: δ 7.34-7.25 (2H, m); 7.23-7.10 (2H, m); 6.88-6.81 (2H, m); 6.77-6.70 (1H, m); 6.54 (1H, d); 5.00-4.86 (1H, m); 4.47 (1H, br s); 4.21 (1H, dd); 3.92 (3H, s); 2.73-2.64 (1H, m); 2.20 (3H, s); 1.40-1.28 (1H, m); 1.17 (3H, d).

cis -1-Acetyl-1,2,3,4-tetrahydro-*N*-(4-methoxyphenyl)-2-methyl-4-quinolinamine (Compound No. 25 Table I).

^{1}H NMR $CDCl_3$: δ 7.36-7.09 (4H, m); 6.79 (2H, d); 6.64-6.57 (2H, m); 4.96-4.82 (1H, m); 4.13 (1H, dd); 3.74 (3H, s); 2.68-2.59 (1H, m); 2.17 (3H, s); 1.28-1.10 (4H, m).

cis -1-Acetyl-1,2,3,4-tetrahydro-2-methyl-*N*-(3-methylphenyl)- 4-quinolinamine (Compound No. 26 Table I).

^{1}H NMR $CDCl_3$: δ 7.37-7.03 (5H, m); 6.58 (1H, d); 6.51-6.41 (2H, m); 4.96-4.82 (1H, m); 4.21 (1H, dd); 2.69-2.59 (1H, m); 2.27 (3H, s); 2.18 (3H, s); 1.30-1.19 (1H, m); 1.15 (3H, d).

(2S*,4R*)-1-Acetyl-2-methyl-*N*-(4-methylphenyl)-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 27 Table I). $[\alpha]_D^{20} = 183°$ (c = 0.36, CH_2Cl_2);

^{1}H NMR $CDCl_3$: δ 7.36-7.08 (4H, m); 7.00 (2H, d); 6.56 (2H, d); 4.96-4.82 (1H, m); 4.17 (1H, dd); 2.68-2.59 (1H, m); 2.24 (3H, s); 2.18 (3H, s); 1.30-1.10 (4H, m).

cis -1-Acetyl-*N*-(2-chloro-4-methylphenyl)-2-methyl-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 28 Table I).

^{1}H NMR $CDCl_3$: δ 7.32-7.08 (5H, m); 6.90 (1H, dd); 6.50 (1H, d); 4.91 (1H, br d); 4.33 (1H, br s); 4.21 (1H, dd); 2.73-2.63 (1H, m); 2.23 (3H, s); 2.18 (3H, s); 1.40-1.27 (1H, m); 1.16 (3H, d).

cis -1-Acetyl-*N*-(4-chloro-2-methylphenyl)-2-methyl-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 29 Table I).

^{1}H NMR $CDCl_3$: δ 7.32-6.98 (6H, m); 6.41 (1H, d); 4.92 (1H, br d); 4.25-4.15 (1H, m); 3.63 (1H, br d); 2.72-2.62 (1H, m); 2.21 (3H, s); 2.18 (3H, s); 1.39-1.27 (1H, m); 1.16 (3H, d).

cis -1-Acetyl-*N*-(2,3-dichlorophenyl)-2-methyl-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 30 Table I).

^{1}H NMR $CDCl_3$: δ 7.33-7.12 (4H, m); 7.02 (1H, t); 6.84 (1H, dd); 6.48 (1H, d); 4.93 (1H, br s); 4.64 (1H, br d); 4.28-4.20 (1H, m); 2.74-2.65 (1H, m); 2.18 (3H, s); 1.44-1.31 (1H, m); 1.16 (3H, d).

cis -1-Acetyl-*N*-(2,4-dichlorophenyl)-2-methyl-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 31 Table I).

^{1}H NMR $CDCl_3$: δ 7.34-7.10 (5H, m); 7.06 (1H, dd); 6.50 (1H, d); 4.92 (1H, br s); 4.46 (1H, br d); 4.24-4.16 (1H, m); 2.73-2.64 (1H, m); 2.18 (3H, s); 1.36 (1H, q); 1.16 (3H, d).

cis -1-Acetyl-*N*-(2,5-dichlorophenyl)-2-methyl-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 32 Table I).

^{1}H NMR $CDCl_3$: δ 7.34-7.12(5H, m); 6.65(1H, dd); 6.55(1H, d); 4.98-4.86(1H, m); 4.53(1H, br d); 4.26-4.17(1H, m); 2.74-2.64(1H, m); 2.21(3H, s); 1.36(1H, q); 1.17(3H, d).

cis -1-Acetyl-*N*-(3,4-dichlorophenyl)-2-methyl-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 33 Table I).

^{1}H NMR $CDCl_3$: δ 7.33-7.10 (5H, m); 6.70 (1H, d); 6.47 (1H, dd); 4.97-4.84 (1H, m); 4.14 (1H, dd); 2.68-2.58 (1H, m); 2.18 (3H, s); 1.32-1.20 (1H, m); 1.15 (3H, d).

cis -1-Acetyl-*N*-(3,5-dichlorophenyl)-2-methyl-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 34 Table I).

^{1}H NMR $CDCl_3$: δ 7.34-7.11 (4H, m); 6.72 (1H, t); 6.49 (2H, d); 4.96-4.84 (1H, m); 4.21-4.12 (1H, m); 4.06-3.96 (1H, m); 2.68-2.58 (1H, m); 2.20 (3H, s); 1.33-1.20 (1H, m); 1.15 (3H, d).

cis -1-Acetyl-*N*-(4-cyclohexylphenyl)-2-methyl-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 35 Table I).

^{1}H NMR $CDCl_3$: δ 7.36 (1H, d); 7.30-7.08 (3H, m); 7.03 (2H, d); 6.59 (2H, d); 4.94-4.81 (1H, m); 4.17 (1H, dd); 3.76 (1H, br s); 2.68-2.58 (1H, m); 2.44-2.34 (1H, m); 2.17 (3H, s); 1.90-1.18 (11H, m); 1.14 (3H, d).

cis -1-Acetyl-*N*-(1,3-benzodioxol-5-yl)-2-methyl-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 37 Table I).

^{1}H NMR $CDCl_3$: δ 7.37-7.08 (4H, m); 6.65 (1H, d); 6.28 (1H, d); 6.08 (1H, dd); 5.87 (2H, s); 4.89 (1H, br d); 4.30-3.98 (2H, m); 2.68-2.57 (1H, m); 2.18 (3H, s); 1.22 (1H, q); 1.14 (3H, d).

cis -1-Acetyl-6-chloro-2-methyl-*N*-(4-methylphenyl)-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 38 Table I).

^{1}H NMR $CDCl_3$: δ 7.34 (1H, s); 7.27-7.22 (1H, m); 7.10-6.97 (3H, m); 6.55 (2H, d); 4.85 (1H, br s); 4.12 (1H, dd); 2.68-2.58 (1H, m); 2.25 (3H, s); 2.16 (3H, s); 1.30-1.18 (1H, m); 1.14 (3H, d).

cis -1-Acetyl-6-chloro-2-methyl-*N*-[4-(4-morpholinyl)phenyl]-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 39 Table I).

^{1}H NMR $CDCl_3$: δ 7.28 (1H, s); 7.22-7.16 (1H, m); 7.06-6.96 (1H, m); 6.86-6.73 (2H,m); 6.55 (2H, br d); 4.79 (1H, br s); 4.03 (1H, br d); 3.80 (4H, br s); 2.98 (4H, br s); 2.62-2.52 (1H, m); 2.10 (3H, s); 1.24-1.03 (4H, m).

cis -1-Acetyl-*N*-(4-methoxyphenyl)-2,6-dimethyl-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 40 Table I).

^{1}H NMR $CDCl_3$: δ 7.17 (1H, s); 7.11-6.98 (2H, m); 6.81 (2H, d); 6.63 (2H, d); 4.88 (1H, br s); 4.11 (1H, dd); 3.77 (3H, s); 3.54 (1H, br s); 2.68-2.58 (1H, m); 2.34 (3H, s); 2.17 (3H, s); 1.27-1.10 (4H, m).

cis -1-Acetyl-6-chloro-*N*-(4-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 41 Table I).

^{1}H NMR $CDCl_3$: δ 7.34 (1H, d); 7.28-7.22 (1H, m); 7.13-7.01 (1H, m); 6.80 (2H, d); 6.59 (2H, d); 4.84 (1H, br s); 4.07 (1H, dd); 3.75 (3H, s); 2.68-2.58 (1H, m); 2.16 (3H, s); 1.28-1.10 (4H, m).

cis -1-Acetyl -4-[[4-(ethoxycarbonyl)phenyl]amino]-1,2,3,4-tetrahydro-2-methyl- 6-quinolinecarboxylic acid ethyl ester (Compound No. 42 Table I).
^{1}H NMR $CDCl_3$: δ 7.99 (1H, dd); 7.94-7.86 (3H, m); 7.23 (1H, d); 6.62 (2H, d); 4.94-4.82 (1H, m); 4.38-4.25 (5H, m); 2.74-2.64 (1H, m); 2.21 (3H, s); 1.39-1.27 (7H, m); 1.17 (3H, d).

cis -4-{[1-Acetyl-2-ethyl-1,2,3,4-tetrahydro-4-quinolinyl]amino}benzonitrile (Compound No. 43 Table I).
^{1}H NMR $CDCl_3$: δ 7.45 (2H, d); 7.31 (1H, dt); 7.23-7.08 (3H, m); 6.60 (2H, d); 4.87 (1H, br s); 4.35 (1H, d); 4.31-4.22 (1H, m); 2.71-2.61 (1H, m); 2.17 (3H, s); 1.64-1.22 (3H, m); 0.86 (3H, t).

cis -1-Acetyl-1,2,3,4-tetrahydro-2-methyl-4-[[4-[(1-methylethoxy)carbonyl]-phenyl]amino]-6-quinolinecarboxylic acid 1-methylethyl ester (Compound No. 44 Table I).
^{1}H NMR $CDCl_3$: δ 7.97 (1H, dd); 7.93-7.86 (3H, m); 7.22 (1H, d); 6.63 (2H, d); 5.24-5.12 (2H, m); 4.94-4.83 (1H, m); 4.34 (1H, dd); 2.74-2.65 (1H, m); 2.20 (3H, s); 1.38-1.23 (13H, m); 1.17 (3H, d).

cis -1-Acetyl-*N*-(4-chlorophenyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 45 Table I).
^{1}H NMR $CDCl_3$: δ 7.19-7.02 (3H, m); 6.88-6.78 (2H, m); 6.58 (2H, br s); 4.93 (1H, br s); 4.13 (1H, dd); 3.75 (3H, s); 2.68-2.58 (1H, m); 2.16 (3H, s); 1.31-1.18 (1H, m); 1.13 (3H, d).

cis -1-Acetyl-6-methoxy-2-methyl-*N*-(4-methylphenyl)-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 46 Table I).

^{1}H NMR $CDCl_3$: δ 7.10-6.92 (4H, m); 6.80 (1H, dd); 6.64 (2H, br s); 4.90 (1H, br s); 4.16 (1H, dd); 3.75 (3H, s); 2.68-2.58 (1H, m); 2.26 (3H, s); 2.15 (3H, s); 1.30-1.17 (1H, m); 1.12 (3H, d).

cis -4-{[1-Acetyl-6-methoxy-2-methyl-1,2,3,4-tetrahydro-4-quinolinyl]amino}-phenyl)(phenyl)methanone (Compound No. 47 Table I).

^{1}H NMR $CDCl_3$: δ 7.80-7.71 (4H, m); 7.57-7.42 (3H, m); 7.09 (1H, br d); 6.86-6.79 (2H, m); 6.66 (2H, d); 4.97 (1H, br s); 4.30 (1H, dd); 3.75 (3H, s); 2.73-2.63 (1H, m); 2.17 (3H, s); 1.38-1.23 (1H, m); 1.16 (3H, d).

cis -4-{[1-Acetyl-6-chloro-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]amino} benzoic acid methyl ester (Compound No. 48 Table I).

^{1}H NMR $CDCl_3$: δ 7.89 (2H, d); 7.30-7.17 (2H, m); 7.10 (1H, br d); 6.59 (2H, d); 4.89 (1H, br s); 4.29-4.18 (2H, m); 3.86 (3H, s); 2.71-2.62 (1H, m); 2.18 (3H, s); 1.38-1.24 (1H, m); 1.15 (3H, d).

cis -1-(4-{[1-Acetyl-6-methoxy-2-methyl-1,2,3,4-tetrahydro-4-quinolinyl]amino}-phenyl)ethanone (Compound No. 49 Table I).

^{1}H NMR $CDCl_3$: δ 7.86 (2H, d); 7.08 (1H, br d); 6.86-6.75 (2H, m); 6.63 (2H, d); 4.96 (1H, br s); 4.29 (1H, dd); 3.74 (3H, s); 2.71-2.62 (1H, m); 2.52 (3H, s); 2.18 (3H, s); 1.36-1.23 (1H, m); 1.15 (3H, d).

cis -4-{[1-Acetyl-6-methoxy-2-methyl-1,2,3,4-tetrahydro-4-quinolinyl]amino}-benzamide (Compound No. 50 Table I).

^{1}H NMR $CDCl_3$: δ 7.70 (2H, d); 7.08 (1H, br d); 6.86-6.76 (2H, m); 6.64 (2H, d); 6.18 (2H, br s); 4.96 (1H, br s); 4.26 (1H, dd); 3.74 (3H, s); 2.70-2.61 (1H, m); 2.18 (3H, s); 1.35-1.21 (1H, m); 1.15 (3H, d).

cis -4-{[1-Acetyl-6-methoxy-2-methyl-1,2,3,4-tetrahydro-4-quinolinyl]amino}-benzonitrile (Compound No. 51 Table I).

^{1}H NMR $CDCl_3$: δ 7.45 (2H, d); 7.14-7.03 (1H, m); 6.81 (1H, dd); 6.71 (1H, d); 6.61 (2H, d); 4.94 (1H, br s); 4.32-4.16 (2H, m); 3.73 (3H, s); 2.68-2.59 (1H, m); 2.16 (3H, s); 1.34-1.22 (1H, m); 1.14 (3H, d).

cis -4-[{1-Acetyl-1,2,3,4-tetrahydro-6-methoxy-2-methyl-4-quinolinyl}amino]-, benzoic acid methyl ester (Compound No. 52 Table I).

^{1}H NMR $CDCl_3$: δ 7.86 (2H, d); 7.05 (1H, br d); 6.82-6.73 (2H, m); 6.60 (2H, d); 4.93 (1H, br s); 4.40-4.18 (2H, m); 3.84 (3H, s); 3.70 (3H, s); 2.68-2.58 (1H, m); 2.15 (3H, s); 1.32-1.19 (1H, m); 1.13 (3H, d).

cis -4-{[1-Acetyl-2,8-dimethyl-1,2,3,4-tetrahydro-4-quinolinyl]amino}benzonitrile (Compound No. 53 Table I).

^{1}H NMR $CDCl_3$: δ 7.44 (2H, d); 7.27-7.12 (2H, m); 7.00 (1H, d); 6.58 (2H, d); 5.23-5.12 (1H, m); 4.33 (1H, br d); 4.19-4.10 (1H, m); 2.72-2.63 (1H, m); 2.27 (3H, s); 1.95 (3H, s); 1.21-1.13 (1H, m); 1.06 (3H, d).

cis -1-Acetyl-6-methoxy-2-methyl-*N*-[4-(4-morpholinyl)phenyl]-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 54 Table I).

^{1}H NMR $CDCl_3$: δ 7.04 (1H, br d); 6.94-6.76 (4H, m); 6.64 (2H, d); 4.90 (1H, br s); 4.18-4.07 (1H, m); 3.90-3.81 (5H, m); 3.75 (3H, s); 3.10-2.94 (4H, m); 2.68-2.57 (1H, m); 2.15 (3H, s); 1.24-1.08 (4H, m).

cis -2-{[1-Acetyl-6-chloro-2-methyl-1,2,3,4-tetrahydro-4-quinolinyl]amino}-benzamide (Compound No. 55 Table I).

^{1}H NMR $CDCl_3$: δ 8.24 (1H, d); 7.46 (1H, dd); 7.34-7.20 (3H, m); 7.08 (1H, br s); 6.67 (1H, t); 6.56 (1H, d); 5.84 (2H, br s); 4.88 (1H, br s); 4.23-4.14 (1H, m); 2.73-2.64 (1H, m); 2.18 (3H, s); 1.47-1.33 (1H, m); 1.15 (3H, d).

cis -4-{[1-Acetyl-2-methyl-1,2,3,4-tetrahydro-4-quinolinyl]amino}benzamide (Compound No. 56 Table I).

^{1}H NMR $CDCl_3$: δ 7.69 (2H, d); 7.34-7.13 (4H, m); 6.64 (2H, d); 5.93 (2H, br s); 4.95 (1H, br d); 4.34-4.22 (2H, m); 2.73-2.64 (1H, m); 2.21 (3H, s); 1.32 (1H, q); 1.18 (3H, d).

cis -4-{[1-Acetyl-2,6-dimethyl-1,2,3,4-tetrahydro-4-quinolinyl]amino}benzonitrile (Compound No. 57 Table I).

^{1}H NMR $CDCl_3$: δ 7.47 (2H, d); 7.16-6.93 (3H, m); 6.63 (2H, d); 4.93 (1H, br s); 4.33-4.19 (2H, m); 2.70-2.60 (1H, m); 2.32 (3H, s); 2.18 (3H, s); 1.31 (1H, q); 1.16 (3H, d).

cis -1-Acetyl-1,2,3,4-tetrahydro-2,6-dimethyl-N-[4-(4-morpholinyl)phenyl]- 4-quinolinamine (Compound No. 58 Table I).

^{1}H NMR $CDCl_3$: δ 7.17 (1H, s); 7.11-6.99 (2H, m); 6.86 (2H, d); 6.64 (2H, d); 4.89 (1H, br s); 4.13 (1H, dd); 3.86 (4H, t); 3.57 (1H, br s); 3.05 (4H, t); 2.68-2.58 (1H, m); 2.32 (3H, s); 2.16 (3H, s); 1.29-1.10 (4H, m).

cis -2-{[1-Acetyl-2-methyl-1,2,3,4-tetrahydro-4-quinolinyl]amino}benzamide (Compound No. 59 Table I).

^{1}H NMR $CDCl_3$: δ 8.27 (1H, d); 7.44 (1H, d); 7.34-7.06 (4H, m); 6.70-6.59 (2H, m); 5.73 (2H, br s); 4.92 (1H, br s); 4.31-4.21 (1H, m); 2.75-2.65 (1H, m); 2.18 (3H, s); 1.38 (1H, q); 1.15 (3H, d).

cis -*N*-(4-{[1-Acetyl-2-methyl-1,2,3,4-tetrahydro-4-quinolinyl]amino}phenyl)-acetamide (Compound No. 60 Table I).

^{1}H NMR $CDCl_3$: δ 7.32-7.08 (5H, m); 7.02-6.90 (1H, br s); 6.59 (2H, d); 4.90 (1H, br d); 4.17 (1H, br d); 3.76 (1H, br s); 2.70-2.59 (1H, m); 2.18 (3H, s); 2.13 (3H, s); 1.32-1.10 (4H, m).

cis -*N*-(4-{[1-Acetyl-6-chloro-2-methyl-1,2,3,4-tetrahydro-4-quinolinyl]amino}-phenyl)acetamide (Compound No. 61 Table I).

^{1}H NMR $CDCl_3$: δ 7.33-6.91 (5H, m); 6.63-6.54 (2H, d); 4.86 (1H, br s); 4.12 (1H, br d); 3.71 (1H, br s); 2.69-2.59 (1H, m); 2.17 (3H, s); 2.14 (3H, s); 1.32-1.09 (4H, m).

cis -4-[{1-Acetyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl}amino]-benzoic acid methyl ester (Compound No. 62 Table I).

^{1}H NMR $CDCl_3$: δ 7.88 (2H, d); 7.33-7.12 (4H, m); 6.60 (2H, d); 4.93 (1H, br d); 4.34-4.20 (2H, m); 3.85 (3H, s); 2.72-2.63 (1H, m); 2.19 (3H, s); 1.31 (1H, q); 1.16 (3H, d).

cis -*N*-(4-{[1-Acetyl-6-methoxy-2-methyl-1,2,3,4-tetrahydro-4-quinolinyl]amino}-phenyl)acetamide (Compound No. 63 Table I).

^{1}H NMR $CDCl_3$: δ 7.33-7.25 (2H, m); 7.12-6.77 (4H, m); 6.61 (2H, d); 4.92 (1H, br s); 4.15 (1H, dd); 3.75 (3H, s); 2.69-2.59 (1H, m); 2.16 (6H, s); 1.30-1.07 (4H, m).

cis -1-Acetyl-1,2,3,4-tetrahydro-6-methoxy-2-methyl-*N*-[4-(methylsulfonyl)phenyl]- 4-quinolinamine (Compound No. 64 Table I).

^{1}H NMR $CDCl_3$: δ 7.73 (2H, d); 7.08 (1H, br d); 6.82 (1H, dd); 6.73 (1H, br d); 6.67 (2H, d); 4.95 (1H, br s); 4.36-4.20 (2H, m); 3.74 (3H, s); 3.01 (3H, s); 2.69-2.60 (1H, m); 2.17 (3H, s); 1.36-1.22 (1H, m); 1.14 (3H, d).

1-[(2S*,4R*)-4-(4-benzoylanilino)-6-bromo-2-methyl-3,4-dihydro-1(2*H*)-quinolinyl]-1-ethanone (Compound No. 65 Table I). $[\alpha]_D^{20} = 132°$ (c = 0.8, CH_2Cl_2).

^{1}H NMR MeOD (two protons is obscured by the H_2O-signal): δ 7.73-7.64 (4H, m); 7.60-7.44 (4H, m); 7.31 (1H, dd); 7.24 (1H, br d); 6.73 (2H, d); 4.39 (1H, dd); 2.72-2.63 (1H, m); 2.19 (3H, s); 1.43-1.30 (1H, m); 1.16 (3H, d).

cis -1-Acetyl-1,2,3,4-tetrahydro-*N*-(4-methoxyphenyl)-2-methyl-6-(4-morpholinyl)- 4-quinolinamine (Compound No. 66 Table I).

^{1}H NMR $CDCl_3$: δ 7.03 (1H, br d); 6.96 (1H, br d); 6.83-6.76 (3H, m); 6.63 (2H, d); 4.88 (1H, br s); 4.10 (1H, dd); 3.83 (4H, t); 3.77 (3H, s); 3.51 (1H, br s); 3.17-3.04 (4H, m); 2.66-2.58 (1H, m); 2.16 (3H, s); 1.26-1.11 (4H, m).

cis -4-{[1-Acetyl-2-methyl-6-(4-morpholinyl)-1,2,3,4-tetrahydro-4-quinolinyl]-amino}benzonitrile (Compound No. 67 Table I).

^{1}H NMR $CDCl_3$: δ 7.45 (2H, d); 7.09 (1H, br d); 6.86 (1H, dd); 6.78 (1H, br s); 6.63 (2H, d); 4.91 (1H, br s); 4.27-3.92 (2H, m); 3.83 (4H, t); 3.16-3.01 (4H, m); 2.68-2.58 (1H, m); 2.18 (3H, s); 1.30 (1H, q); 1.14 (3H, d).

cis -1-Acetyl-1,2,3,4-tetrahydro-2-methyl-6-(4-morpholinyl)-*N*-phenyl-4-quinolinamine (Compound No. 68 Table I).

^{1}H NMR $CDCl_3$: δ 7.25-6.64 (8H, m); 4.90 (1H, br s); 4.19 (1H, dd); 3.82 (4H, t); 3.19-3.02 (4H, m); 2.67 (1H, m); 2.17 (3H, s); 1.33-1.10 (4H, m).

cis -4-[{1-Acetyl-2-ethyl-1,2,3,4-tetrahydro-4-quinolinyl}amino]-benzoic acid methyl ester (Compound No. 69 Table I).

^{1}H NMR $CDCl_3$: δ 7.88 (2H, d); 7.32-7.07 (4H, m); 6.59 (2H, d); 4.86 (1H, br s); 4.30 (1H, dd); 3.85 (3H, s); 2.72-2.62 (1H, m); 2.18 (3H, s); 1.74-1.26 (3H, m); 0.86 (3H, t).

cis -1-Acetyl-1,2,3,4-tetrahydro-*N*,2-diphenyl-4-quinolinamine (Compound No. 70 Table I).

^{1}H NMR $CDCl_3$: δ 7.43-7.14 (11H, m); 6.80 (1H, t); 6.70 (2H, d); 5.81 (1H, br s); 4.42 (1H, dd); 3.85 (1H, br s); 2.93-2.84 (1H, m); 2.23 (3H, s); 1.78 (1H, q).

cis -1-Acetyl-1,2,3,4-tetrahydro-2-methyl-6-(methylthio)-*N*-phenyl-4-quinolinamine (Compound No. 72 Table I).

^{1}H NMR $CDCl_3$: δ 7.30-6.99 (5H, m); 6.76 (1H, t); 6.64 (2H, d); 4.87 (1H, br s); 4.24-4.12 (1H, m); 3.75 (1H, br d); 2.70-2.58 (1H, m); 2.38 (3H, s); 2.16 (3H, s); 1.33-1.05 (4H, m).

cis -1-Acetyl -1,2,3,4-tetrahydro-2-methyl-6-(methylsulfonyl)-*N*-phenyl-4-quinolinamine (Compound No. 73 Table I).

^{1}H NMR $CDCl_3$: δ 7.96-7.88 (2H, m); 7.39 (1H, d); 7.22 (2H, t); 6.80 (1H, t); 6.65 (2H, d); 4.90-4.78 (1H, m); 4.32-4.23 (1H, m); 3.83 (1H, br d); 3.03 (3H, s); 2.79-2.69 (1H, m); 2.26 (3H, s); 1.41-1.29 (1H, m); 1.21 (3H, d).

(2S*,4R*)-1-Acetyl -1,2,3,4-tetrahydro-6-iodo-2-methyl-*N*-phenyl-4-quinolinamine (Compound No. 74 Table I). $[\alpha]_D^{20} = 309°$ (c = 0.6, CH_3Cl).

^1H NMR $CDCl_3$: δ 7.67 (1H, br s); 7.63 (1H, dd); 7.23 (2H, dt); 6.90 (1H, br d); 6.79 (1H, t); 6.64 (2H, d); 4.86 (1H, br d); 4.17 (1H, br d); 3.74 (1H, br s); 2.69-2.59 (1H, m); 2.19 (3H, s); 1.35-1.22 (1H, m); 1.16 (3H, d).

(2S,4R)-1-Acetyl-6-bromo-2-methyl-N-phenyl-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 75 Table I). $[\alpha]_D^{20} = 278°$ (c = 0.11, CH_2Cl_2).

^1H NMR $CDCl_3$: δ 7.48 (1H, m); 7.43 (1H, dd); 7.28-7.18 (2H, m); 7.08-6.98 (1H, d); 6.79 (1H, t); 6.64 (2H, d); 4.92-4.80 (1H, s); 4.18 (1H, dd); 3.90-3.70 (1H, s); 2.71-2.60 (1H, m); 2.18 (3H, s); 1.32-1.19 (1H, m); 1.17 (3H, d).

trans -1-Acetyl -1,2,3,4-tetrahydro-2-methyl-*N*-phenyl-4-quinolinamine (Compound No. 1 Table II).

^1H NMR $CDCl_3$: δ 7.41 (1H, dd); 7.32-7.12 (5H, m); 6.74-6.62 (3H, m); 4.92 (1H, d); 4.61 (1H, d); 3.85 (1H, s); 2.56-2.46 (1H, m); 2.18 (3H, s); 1.81-1.72 (1H, m); 1.20 (3H, d).

trans -1-Acetyl -1,2,3,4-tetrahydro-4-[[4-(methoxycarbonyl)phenyl]amino]-2-methyl- 6-quinolinecarboxylic acid methyl ester (Compound No. 18 Table II).

^1H NMR $CDCl_3$: δ 8.10 (1H, d); 7.98 (1H, dd); 7.86 (2H, d); 7.37 (1H, d); 6.62 (2H, d); 4.92-4.84 (1H, m); 4.76-4.71 (1H, t); 4.40-4.30 (1H, s br); 3.91 (3H, s); 3.84 (3H, s); 2.50-2.42 (1H, m); 2.21 (3H, s); 1.96-1.88 (1H, m); 1.22 (3H, d).

trans -1-Acetyl -N-(2-chlorophenyl)-2-methyl-1,2,3,4-tetrahydro-4-quinolinamine (Compound No. 21 Table II).

^1H NMR $CDCl_3$: δ 7.45-7.18 (6H, m); 6.86 (1H, d); 6.62 (1H, dd); 4.99-4.92 (1H, m); 4.76-4.60 (2H, m); 2.65-2.58 (1H, m); 2.20 (3H, s); 1.81-1.76 (1H, m); 1.01 (3H, d).

trans -1-Acetyl -*N*-(4-bromophenyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinamine (Compound No. 24 Table II).

^{1}H NMR $CDCl_3$: δ 7.42 (6H, m); 6.53 (2H, d); 5.0-4.85 (1H, d br); 4.55 (1H, t); 2.58-2.49 (1H, m); 2.18 (3H, s); 1.80-1.72 (1H, m); 1.19 (3H, d).

cis-1-Acetyl -1,2,3,4-tetrahydro-2-methyl-N-(2-pyrazinyl)- 4-quinolinamine (Compound No. 1 Table III).

^{1}H NMR $CDCl_3$: δ 8.05-7.99 (2H, m); 7.92 (1H, d); 7.38-7.15 (4H, m); 5.01-4.90 (1H, m); 4.90-4.82 (1H, m); 4.72 (1H, d); 2.73-2.62 (1H, m); 2.18 (3H, s); 1.38-1.25 (1H, m); 1.19 (3H, d).

cis -1-Acetyl -6-chloro-1,2,3,4-tetrahydro-2-methyl-N-(2-pyrazinyl)- 4-quinolinamine (Compound No. 2 Table III).

^{1}H NMR $CDCl_3$: δ 8.04-8.01 (2H, m); 7.93 (1H, d); 7.28 (1H, dd); 7.23 (1H, dd); 7.11 (1H, d); 4.98-4.80 (2H, m); 4.80-4.78 (1H, m); 2.70

cis -1-Acetyl -1,2,3,4-tetrahydro-2-methyl-N-(4-pyridinyl)- 4-quinolinamine (Compound No. 3 Table III).

-2.62 (1H, m); 2.18 (3H, s); 1.39-1.24 (1H, m); 1.19 (3H, d).

^{1}H NMR CD_3OD: δ 8.27 (2H, d); 7.48-7.45 (2H, m); 7.38-7.29 (1H, m); 7.00 (2H, d); 6.61 (1H, d); 5.41 (1H, dd); 5.02-4.88 (1H, m); 2.93-2.82 (1H, m); 2.21 (3H, s); 2.18-2.00 (1H, m); 1.35 (3H, d).

Biological assay

The ability of the compounds described herein to inhibit STAT6 signaling pathway is manifested in their ability to inhibit STAT6 driven reporter gene activity.

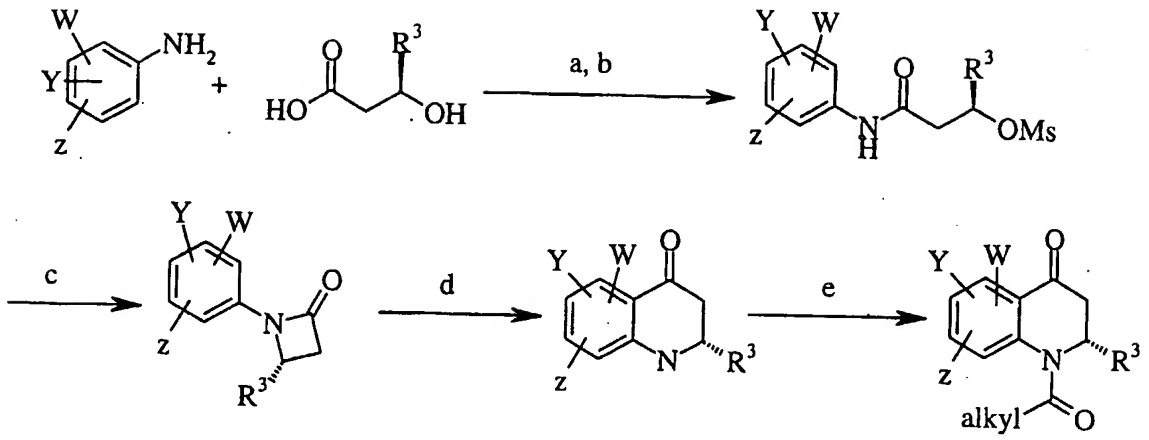
The cytokine-responsive human cell line U937 were transfected with a reporter gene plasmid consisting of an interluekin 4 (IL-4) responsive promoter driving the heterologous firefly gene for luciferase. The reporter gene plasmid also contained a gene for neomycin resistance. The IL-4 responsive promoter were constructed by four oligomerized combined C/BEPβ and STAT6 binding sites with the nucleotide sequence GTTGCTCAATCGACTTCCCAAGAA in close contact with a TATA- box. Cells with a stable integration of the reporter gene plasmid were selected by cultivation in neomycin. Such transfected cells were used for IL-4 induction by adding 10 ng/ml recombinant human IL-4 to 0.5-1 x 10^6 cells per ml. IL-4 induction were carried out for 4-5 h. Thereafter the cells were lysed and luciferase activity determined by using standard techniques. Numbers measured are the mean fold induction (fold induction for U937 is defined as the luciferase response in an IL-4 treated U937 cell sample divided by the luciferase response in an untreated U937 cell sample). Typically, IL-4 stimulation gave 15-20 fold induction of the luciferase response. Compounds were added 5 min before IL-4 when tested in the reporter gene assay. Compound effect was expressed as the concentration of compound giving 50 percent inhibition (IC50) of the luciferase response to addition of IL-4. The results from compound testing are shown in Table IV.

TABLE IV

Inhibition of STAT6-driven reporter gene activity

Compound	No 27 Table I	No 36 Table I	No 74 Table I
IC50 μM	0.80	0.43	0.18

SCHEME 1



a: N,N dicyclohexyl carbodiimide (DCC), dimethylamino pyridine (DMAP), CH_2Cl_2, 60%;

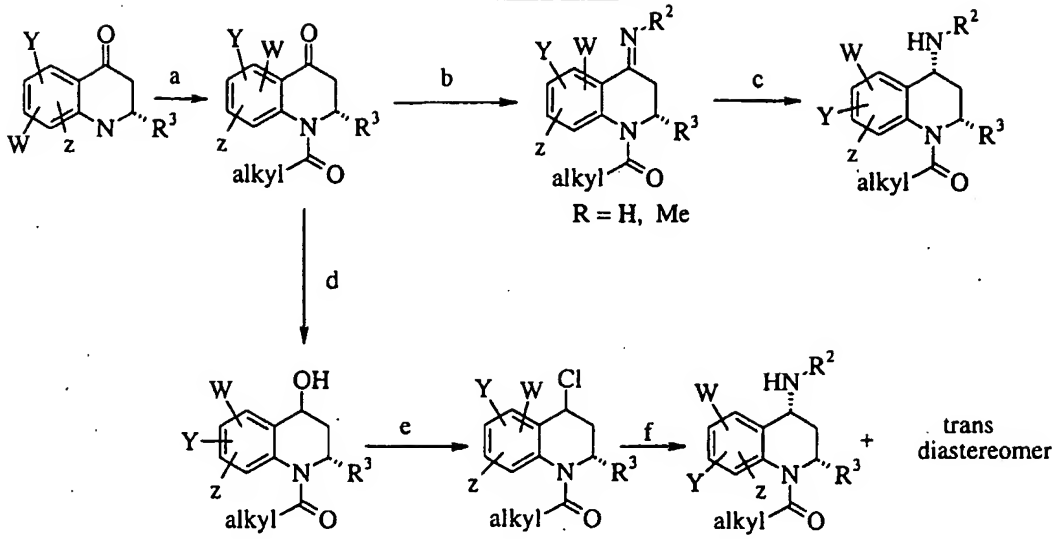
b: Ms_2O, $EtNiPr_2$, CH_2Cl_2, 0 °C, 80-90%;

c: NaH, DMF, CH_2Cl_2, 70%;

d: F_3CCO_2H, 70 °C, 75%;

e: (alkyl)COCl, Et_3N, CH_2Cl_2, 50-60%.

SCHEME 2



a: (alkyl)COCl, Et_3N, CH_2Cl_2, r.t.;

b: R^2NH_2, pTSA, molecular sieve 3Å, Toluene, reflux;

c: H_2 (1 atmosphere), Pd/C, EtOAc;

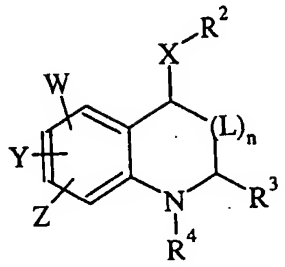
d: $NaBH_4$, MeOH, 0°C;

e: $SOCl_2$, Pyridine, CH_2Cl_2, 0°C;

f: R^2NH_2, MeCN, 80°C.

CLAIMS

1. A compound of formula (I):



(I)

wherein:

L is CH_2, O or S;

n is 0 or 1;

W, Y and Z are, independently hydrogen, cyano, nitro, halogen, N_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONR^5R^6$, COR^{10}, SO_2R^{12}, methylenedioxy, $NHCOR^{11}$ or heterocyclyl;

R^2 is aryl or heteroaryl optionally substituted by cyano, nitro, halogen, N_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONR^{13}R^{14}$, COR^{15}, SO_2R^{16}, methylenedioxy, $NHCOR^{17}$ or heterocyclyl;

R^3 is C_{1-4} alkyl or C_{1-4} haloalkyl;

R^4 is $CO(C_{1-4}$ alkyl) or $CO(C_{1-4}$ haloalkyl);

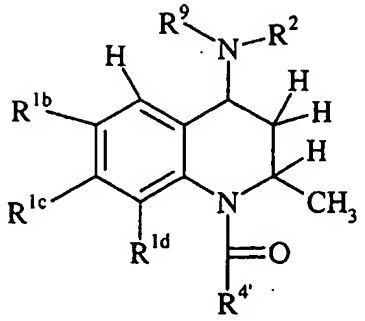
X is O, S, SO, SO_2, CR^7R^8 or NR^9;

R^5, R^6, R^7, R^8, R^{13} and R^{14} are, independently, hydrogen or C_{1-6} alkyl;

R^9 is hydrogen, C_{1-6} alkyl or $CO(C_{1-4}$ alkyl);

R^{10}, R^{11}, R^{12}, R^{15}, R^{16} and R^{17} are, independently, C_{1-6} alkyl or phenyl;

or a pharmaceutically acceptable salt thereof; or a solvate thereof; provided that the compound of formula (I) is not a compound of formula (Iz):



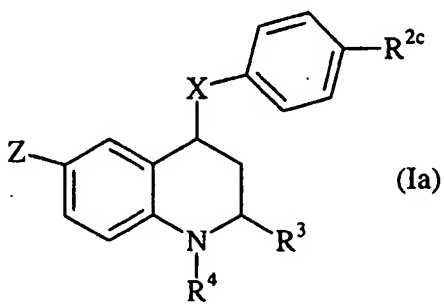
(Iz)

wherein

R^{1b}	R^{1d}	R^{1c}	$R^{4'}$	R^2	R^9
H	H	H	n-butyl	C_6H_5	H
H	H	H	n-propyl	C_6H_5	$COCH_3$
H	H	H	n-propyl	C_6H_5	H
H	H	H	Ethyl	C_6H_5	H
Br	H	H	Methyl	C_6H_5	$COCH_3$
Methyl	H	H	Methyl	4-CH_3-C_6H_4	H
Methyl	Methyl	H	Methyl	2,4-$(CH_3)_2$-C_6H_3	H
H	H	H	Methyl	C_6H_5	H
NO_2	H	H	Methyl	4-NO_2-C_6H_4	$COCH_3$
NO_2	H	H	Methyl	C_6H_5	$COCH_3$
Cl	H	H	Methyl	C_6H_5	$COCH_3$
H	H	H	Methyl	C_6H_5	$COCH_3$
H	H	H	Methyl	2,4-Br_2-C_6H_3	$COCH_3$

in free base or unsolvated form.

2. A compound of formula (Ia):



(Ia)

wherein Z, R^3, R^4 and X are as defined in claim 1, and R^{2c} is hydrogen, cyano, nitro, halogen, N_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONR^{13}R^{14}$, COR^{15}, SO_2R^{16}, methylenedioxy, $NHCOR^{17}$ or heterocyclyl; wherein R^{13}, R^{14}, R^{15}, R^{16} and R^{17} are as defined in claim 1; or a pharmaceutically acceptable salt thereof; or a solvate thereof.

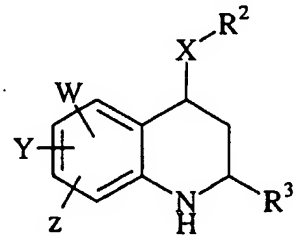
3. A compound as claimed in claim 1 or 2 wherein X is NH.

4. A compound as claimed in claim 1, 2 or 3 wherein R^3 is methyl.

5. A compound as claimed in claim 1, 2, 3 or 4 wherein R^4 is $C(O)CH_3$.

6. A compound as claimed in claim 1, 3, 4 or 5 wherein R^2 is is phenyl para-substituted by $C(O)_2CH_3$, iodo, N_3, bromo, methyl, $C(O)_2CH_2CH_3$, cyano or methoxy.

7. Processes for the preparation of a compound of formula (I) as claimed in claim 1 by reacting a compound of formula (II):

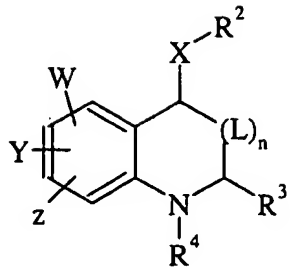


(II)

with acetic anhydride in the presence of a base at room temperature.

8. A pharmaceutical composition which comprises a compound of the formula (I) as claimed in claim 1 or 2, or a pharmaceutically acceptable salt thereof or solvate thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

9. A compound of formula (I):



(I)

wherein:

L is CH_2, O or S;

n is 0 or 1;

W, Y and Z are, independently hydrogen, cyano, nitro, halogen, N_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONR^5R^6$, COR^{10}, SO_2R^{12}, methylenedioxy, $NHCOR^{11}$ or heterocyclyl;

R^2 is aryl or heteroaryl optionally substituted by cyano, nitro, halogen, N_3, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{3-6} cycloalkyl, CO_2H, $CO_2(C_{1-6}$ alkyl), $CONR^{13}R^{14}$, COR^{15}, SO_2R^{16}, methylenedioxy, $NHCOR^{17}$ or heterocyclyl;

R^3 is C_{1-4} alkyl or C_{1-4} haloalkyl;

R^4 is $CO(C_{1-4}$ alkyl) or $CO(C_{1-4}$ haloalkyl);

X is O, S, SO, SO_2, CR^7R^8 or NR^9;

R^5, R^6, R^7, R^8, R^{13} and R^{14} are, independently, hydrogen or C_{1-6} alkyl;

R^9 is hydrogen, C_{1-6} alkyl or $CO(C_{1-4}$ alkyl);

R^{10}, R^{11}, R^{12}, R^{15}, R^{16} and R^{17} are, independently, C_{1-6} alkyl or phenyl;

or a pharmaceutically acceptable salt thereof; or a solvate thereof, for use in medical therapy.

10. A compound of formula (I) as defined in claim 8, or a pharmaceutically acceptable salt thereof or solvate thereof, in the manufacture of a medicament for use in therapy.

11. A method of treating a STAT6 signal pathway mediated disease state in a mammal which comprises administering to a mammal in need of such treatment

an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof; or a solvate thereof, as claimed in claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00597

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 215/42, C07D 401/12, C07D 251/46, A61K 31/47, A61P 11/00, A61P 17/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0017165 A1 (PFIZER PRODUCTS INC.), 30 March 2000 (30.03.00), CAPLUS RN 261946-91-2, RN 261947-61-9, RN 261947-62-0	1-10
X	WO 0017166 A1 (PFIZER PRODUCTS INC.), 30 March 2000 (30.03.00), CAPLUS RN 262587-41-7, RN 2622587-65-5, RN 2622587-79-1, RN 2622587-82-6	1-10
E,X	WO 0176629 A1 (TAKEDA CHEMICAL INDUSTRIES, LTD.), 18 October 2001 (18.10.01), CAPLUS RN 367508-91-6, RN 367508-90-5, RN 26343-37-3, RN 26343-40-8, RN 367508-34-7	1-10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 June 2002	05 -07- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer FERNANDO FARIETA/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00597

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Journal of the Chemical Society, Perkin transections I, Volume 12, 1980, J.C.S. Perkin I et al: "Catalytic and Non-catalytic Addition of Aromatic Amines to Terminal Acetylenes in the Presence of Mercury (II) Chloride and Acetate", pages 2732-2737, CAPLUS RN 26343-37-3, RN 26343-40-8, RN 76513-13-8, Compound 6	1-10
A	Bulletin of the chemical society of Japan, Volume 42, 1969, Masuo Funabashi et al: "Configuration and Conformation of So-called Bis(alkylidenearylamines" pages 2885-2894, CAPLUS RN 26343-39-5, RN 26343-40-8, RN 26343-42-0, Compound III	1-10
A	Chemical Communications, February, 1969, Volume 119, Robert E. Harmon et al: "Keten Imine-Dimethyl Sulphoxide Oxidation of 2,3-O-Isopropylideneadenosine, page 327, CAPLUS RN 22609-18-3, Compound IV and V	1-10
A	Canadian Journal of Chemistry, Volume 56, No 5, 1978, G.A. Dauphinee et al: "1,2-Dihydroquinolines: preparation and isolation as intermediates in the synthesis of quinolines", pages 632-634, Compounds 3	1-10
A	Chem. Pharm. Bull., Volume 38, No 6, 1990, Minoru Uchida et al: "Synthesis and Antiulcer Activity of 4-Substituted 8-[(2-Benzimidazolyl)-sulfinylmethyl]-1,2,3,4-tetrahydroquinolines and Related Compounds", pages 1575-1586, CAPLUS RN 112645-38-2, IX a-e, chart 6	1-10
A	Tetrahedron Letters, Volume 31, No 14, 1990, Angelo Clerici et al: "Arylative Amination of Aldehydes Promoted by Aqueous Titanium Trichloride", pages 2069-2072, CAPLUS RN 1026-05-7, RN 128854-15-9, Compound 7	1-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/00597

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

International application No.
PCT/SE02/00597

Claim 11 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 02/00597

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0017165 A1	30/03/00	AP 200102100 D	00/00/00
		AU 5440399 A	10/04/00
		BG 105429 A	31/12/01
		BR 9913855 A	24/07/01
		CN 1318057 T	17/10/01
		CZ 20010954 A	12/12/01
		EP 1088325 A	04/04/01
		EP 1114032 A	11/07/01
		HR 20010200 A	30/04/02
		NO 20011349 A	14/05/01
		PL 346830 A	25/02/02
		SK 3532001 A	03/12/01
		TR 200100780 T	00/00/00
		TW 428203 B	00/00/00
		US 6075249 A	13/06/00
		US 6140343 A	31/10/00
		WO 9966528 A	23/12/99
WO 0017166 A1	30/03/00	AU 5439899 A	10/04/00
		BR 9913842 A	12/06/01
		EP 1114033 A	11/07/01
		US 6147090 A	14/11/00
		US 6204576 B	20/03/01
		US 6395751 B	28/05/02
WO 0176629 A1	18/10/01	AU 4684401 A	23/10/01
		JP 2001348332 A	18/12/01